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=> d his

     (FILE 'HOME' ENTERED AT 14:19:58 ON 23 AUG 2005)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 14:20:07 ON 23 AUG 2005
L1             1 S US20040209802/PN OR (US2003-706701# OR EP2002-26342)/AP,PRN
               E LEHMAN P/AU
L2            52 S E3-E7,E9-E12
               E LEHMANN P/AU
L3           267 S E3-E6,E11-E14
               E OREDDIGER R/AU
               E ROEDDIGER R/AU
L4             9 S E3,E4
               E ROEDIGER R/AU
L5             2 S E4
               E RODIGER R/AU
L6             1 S E4
               E RODDIGER R/AU
L7             2 S E4
               E WALTER MATSUI/AU
L8             4 S E4,E5
               E MATSUI R/AU
L9            15 S E3
               E MATSUI W/AU
               SEL RN L1

     FILE 'REGISTRY' ENTERED AT 14:22:38 ON 23 AUG 2005
L10            7 S E1-E7
L11            6 S L10 AND ERYTHROPOIETIN
L12            1 S L10 NOT L11
               E ERYTHROPOIETIN
L13         1792 S E3
L14         1792 S L11,L13
               E IRON/CN
L15            1 S E3
               E FE/MF
L16           30 S E3 NOT MASS
L17           30 S L15,L16

     FILE 'HCAPLUS' ENTERED AT 14:24:56 ON 23 AUG 2005
L18         9810 S L14
L19        11804 S ?ERYTHROPOIETIN?
L20          129 S DARBEPOETIN?(S)(ALPHA OR ALFA)
L21          135 S ?DARBEPOETIN?
L22         6067 S EPO OR EPREX
L23          298 S EPOETIN?(S)(ALFA OR ALPHA)
L24          100 S EPOETIN?(S)BETA
L25          458 S EPOETIN
L26           42 S ARANESP
L27        14463 S L18-L26
L28          655 S L27 AND L17
L29         1236 S L27 AND (FE OR IRON)
L30         1243 S L28,L29
               E HEART DISEASE/CT
               E E4+ALL
               E E2+ALL
L31        86736 S E7+OLD,NT
L32           29 S L30 AND L31
L33            0 S E90+OLD,NT AND L30
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L34          47 S E92+OLD,NT AND L30
L35          36 S L32,L34 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L36           1 S L32,L34 AND L1-L9
L37           3 S L35 AND ?CONJUGAT?
L38           2 S L37 NOT 3/SC
L39           2 S L36,L38
L40          33 S L35 NOT L36-L39
                SEL DN AN 6-9 13-15 19-27
L41          16 S L40 AND E1-E48
L42          18 S L39,L41
L43         597 S ?RHUEPO?
L44         155 S L43 AND (L17 OR FE OR IRON)
L45           3 S L44 AND L31
                E HEART, DISEASE/CT
                E E3+ALL
L46           5 S L44 AND E92+OLD,NT
L47           5 S L45,L46
L48           4 S L47 NOT 2005/PY
L49          19 S L42,L48 AND L1-L9,L18-L48
L50       14474 S L27,L43
L51         360 S L50 AND ?CONJUGAT?
L52         330 S L50 AND ?GLYCOSYLAT?
L53         194 S L50 AND (PEG OR PEGYLAT?)
L54          55 S L50 AND (POLYOXYETHYLENE OR POLYETHYLENEGLYCOL OR POLYETHYLEN
L55           4 S L50 AND POLY()(OXYETHYLENE OR ETHYLENEGLYCOL OR ETHYLENEOXIDE
L56          24 S L50 AND POLY()(OXY ETHYLENE OR ETHYLENE GLYCOL OR ETHYLENE OX
L57         237 S L50 AND (POLYOXY ETHYLENE OR POLYETHYLENE GLYCOL OR POLYETHYL
L58         316 S L50 AND POLYOXYALKYLENE

     FILE 'REGISTRY' ENTERED AT 14:42:28 ON 23 AUG 2005
L59           1 S 25322-68-3
L60           0 S L14 AND C2H4O

     FILE 'HCAPLUS' ENTERED AT 14:42:46 ON 23 AUG 2005
L61         266 S L50 AND L59
L62         986 S L51-L58,L61
L63         804 S L62 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L64          32 S L63 AND (L17 OR FE OR IRON)
L65          30 S L64 AND L18

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L66           1 S L14 AND NC4/ES
L67          11 S L14 AND S/ELS

     FILE 'HCAPLUS' ENTERED AT 14:45:59 ON 23 AUG 2005
L68       12350 S L27 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L69        1036 S L68 AND (L17 OR FE OR IRON)
L70        1808 S L63-L65,L69
L71        1808 S L70 OR L70
L72         500 S L71  RAN=(2001:686932,)
L73         500 S L71  RAN=(1997:740129,2001:679500)
L74         808 S L71  RAN=(,1997:730870)

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     FILE 'HCAPLUS' ENTERED AT 14:48:17 ON 23 AUG 2005
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                SET SMARTSELECT OFF
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                 SET SMARTSELECT OFF

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L78         4980 S L77

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                 SET SMARTSELECT OFF

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L81        49174 S L76,L78,L80
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L84            1 S L83 AND S/ELS
L85           54 S L83 NOT L84
L86              STR
L87           50 S L86
L88              STR L86
L89           50 S L88
L90        15844 S L86 FUL
L91           86 S L90 AND C2H4O
L92           28 S L91 AND 1/NR NOT P/ELS
                 SEL RN 4 6-9 22 28
L93            7 S L92 AND E1-E7
L94           58 S L91 NOT L92
L95           35 S L94 NOT P/ELS

     FILE 'HCAPLUS' ENTERED AT 15:13:34 ON 23 AUG 2005
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L97            0 S L96 AND L50
L98          136 S L51,L52 AND L53-L58,L61
L99          110 S L98 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L100          18 S L99 AND L51 AND L52
L101           0 S L100 AND L31
L102           6 S L98 AND L31
L103           4 S L99 AND L31
L104           6 S L102,L103
L105          18 S L100 NOT L104
                 SEL DN AN 3 7 9 12 13 15 16 17
L106           8 S E8-E31 AND L105
                 SEL DN AN L48 1 4
L107           2 S L48 AND E32-E37
L108          27 S L49,L106,L107
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:23:50 ON 23 AUG 2005
L109          19 S E38-E56
L110          15 S L109 AND L14
L111           3 S L109 AND L17
L112           1 S L109 AND L59

=> d sta que l93
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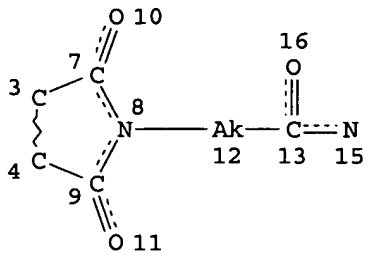
L86 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
L90 15844 SEA FILE=REGISTRY SSS FUL L86
L91 86 SEA FILE=REGISTRY ABB=ON PLU=ON L90 AND C2H4O
L92 28 SEA FILE=REGISTRY ABB=ON PLU=ON L91 AND 1/NR NOT P/ELS
L93 7 SEA FILE=REGISTRY ABB=ON PLU=ON L92 AND (321936-04-3/BI OR 724722-33-2/BI OR 724722-36-5/BI OR 724722-89-8/BI OR 724722-92-3/BI OR 725273-90-5/BI OR 88504-24-9/BI)

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:25:04 ON 23 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 23 Aug 2005 VOL 143 ISS 9
FILE LAST UPDATED: 22 Aug 2005 (20050822/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l108 bib abs hitstr retable tot

L108 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:996201** HCAPLUS
DN **141:422003**
TI Cell-free oligosaccharide remodeling and glycoPEGylation methods and the

proteins/peptides produced
IN De Frees, Shawn; Zopf, David; Bayer, Robert; Bowe, Caryn; Hakes, David; Chen, Xi
PA Neose Technologies, Inc., USA
SO PCT Int. Appl., 1024 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 15

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2004099231	A2	20041118	WO 2004-US11494	20040409	
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	US 2004043446	A1	20040304	US 2003-411037	20030409	<--
	US 2004063911	A1	20040401	US 2003-411026	20030409	<--
	US 2004077836	A1	20040422	US 2003-410962	20030409	<--
	US 2004082026	A1	20040429	US 2003-411049	20030409	<--
	US 2004115168	A1	20040617	US 2003-410930	20030409	<--
	US 2004126838	A1	20040701	US 2003-410997	20030409	<--
	US 2004132640	A1	20040708	US 2003-411012	20030409	<--
	US 2004142856	A1	20040722	US 2003-410913	20030409	<--
	US 2005031584	A1	20050210	US 2003-410980	20030409	<--
	US 2005100982	A1	20050512	US 2003-410897	20030409	<--
PRAI	US 2003-410897	A	20030409			
	US 2003-410913	A	20030409			
	US 2003-410930	A	20030409			
	US 2003-410945	A	20030409			
	US 2003-410962	A	20030409			
	US 2003-410980	A	20030409			
	US 2003-410997	A	20030409			
	US 2003-411012	A	20030409			
	US 2003-411026	A	20030409			
	US 2003-411037	A	20030409			
	US 2003-411043	A	20030409			
	US 2003-411044	A	20030409			
	US 2003-411049	A	20030409			
	US 2001-328523P	P	20011010	<--		
	US 2001-344692P	P	20011019	<--		
	US 2001-334233P	P	20011128	<--		
	US 2001-334301P	P	20011128	<--		
	US 2002-387292P	P	20020607	<--		
	US 2002-391777P	P	20020625	<--		
	US 2002-396594P	P	20020717	<--		
	US 2002-404249P	P	20020816	<--		
	US 2002-407527P	P	20020828	<--		
	WO 2002-US32263	A2	20021009	<--		
	US 2002-287994	A2	20021105	<--		
	US 2003-360770	A2	20030106			
	US 2003-438582P	P	20030106			
	US 2003-360779	A2	20030219			

US 2003-448381P P 20030219

AB The invention includes methods and compns. for remodeling a peptide mol., including the addition or deletion of one or more glycosyl groups to a peptide, and/or the addition of a modifying group to a peptide. In vitro methods for addition and/or deletion of sugars to or from a glypeptide mol. are carried out in a manner as to provide a peptide mol. having a specific customized or desired **glycosylation** pattern, preferably including the addition of a modified sugar. The peptide is enzymically treated in vitro by the systematic addition of the appropriate enzymes and substrates. A key feature of the invention therefore is to take a peptide produced by any cell type and generate a core glycan structure on the peptide, following which the glycan structure is then remodeled in vitro to generate a peptide having a **glycosylation** pattern suitable for therapeutic use in a mammal. The blood-circulation half-life of the selected peptide is extended by **conjugating** the peptide to a synthetic or natural polymer of a size sufficient to retard the filtration of the protein by the glomerulus, as illustrated by **conjugating erythropoietin** to albumin via a **polyethylene glycol** (**PEG**) linker using a combination of chemical and enzymic modifications.

IT **11096-26-7P**, **Erythropoietin**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cell-free oligosaccharide remodeling and glycoPEGylation methods and the proteins/peptides produced)

RN 11096-26-7 HCAPLUS

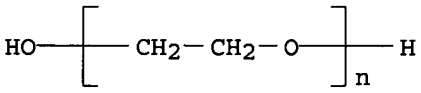
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **25322-68-3**, **Poly(ethylene glycol)**
RL: BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(cell-free oligosaccharide remodeling and glycoPEGylation methods and the proteins/peptides produced)

RN 25322-68-3 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L108 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:467755 HCAPLUS

DN 141:34188

TI Methods for the use of **erythropoietin** and its derivatives for the treatment of heart diseases

IN **Lehmann, Paul**; **Roeddiger, Ralf**; **Walter-Matsui, Ruth**

PA F. Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PI	WO 2004047858	A1	20040610	WO 2003-EP12822	20031117 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004209802	A1	20041021	US 2003-706701	20031112 <--
PRAI	EP 2002-26342	A	20021122 <--		

AB The present invention relates to the use of **erythropoietin** for the treatment of disturbances of **iron** distribution in heart diseases.

IT **702719-61-7**, **Erythropoietin** (human) **702719-62-8**, **Erythropoietin** (human)
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; methods for use of **erythropoietin** (**EPO**) and its derivs. for treatment of heart diseases)

RN 702719-61-7 HCAPLUS
CN Erythropoietin (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 702719-62-8 HCAPLUS
CN Erythropoietin (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **7439-89-6**, **Iron**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(disturbances in cardiac distribution; methods for use of **erythropoietin** (**EPO**) and its derivs. for treatment of heart diseases)

RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

IT **11096-26-7**, **Erythropoietin**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for use of **erythropoietin** (**EPO**) and its derivs. for treatment of heart diseases)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **11096-26-7D**, **Erythropoietin**, **conjugates** and derivs. **113427-24-0**, **Epoetin alfa** **122312-54-3**, **Epoetin beta** **209810-58-2**, **Darbepoetin alfa**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for use of **erythropoietin** (**EPO**) and its derivs. for treatment of heart diseases)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 113427-24-0 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 122312-54-3 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 209810-58-2 HCAPLUS
CN Erythropoietin [30-asparagine,32-threonine,87-valine,88-asparagine,90-threonine] (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
de Valk, B	1999	159	1542	ARCHIVES OF INTERNAL	MEDLINE
Ernst, S	2002			US 2002115833 A1	HCAPLUS
La Roche, H	2003			WO 03025583 A	HCAPLUS
Peeters, H	1999	18	201	RHEUMATOLOGY INTERNA	HCAPLUS
Silverberg, D	2002			US 2002065214 A1	
Thomas, C	2002	48	1066	CLINICAL CHEMISTRY	HCAPLUS

L108 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:333839** HCAPLUS
DN **140:352406**
TI **Erythropoietin glycosylation** and the modification of protein structure and activity for therapeutic use
IN De Frees, Shawn; Zopf, David; Bayer, Robert; Bowe, Caryn; Hakes, David; Chen, Xi
PA Neose Technologies, Inc., USA
SO PCT Int. Appl., 1018 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 15

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004033651	A2	20040422	WO 2003-US31974	20031008 <--
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	WO 2003031464	A2	20030417	WO 2002-US32263	20021009 <--
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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
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UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
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SZ, SZ, TZ, TZ, UG, UG, ZM, ZM, ZW, ZW, AM, AZ, BY, KG, KZ, MD,
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GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM,
GA, GN, GQ

US	2004137557	A1	20040715	US 2002-287994	20021105 <--
CA	2501832	AA	20040422	CA 2003-2501832	20031008 <--
PRAI WO	2002-US32263	A	20021009 <--		
US	2002-287994	A	20021105 <--		
US	2003-360770	A	20030106		
US	2003-360779	A	20030219		
US	2003-410945	A	20030409		
US	2001-328523P	P	20011010 <--		
US	2001-344692P	P	20011019 <--		
US	2001-334233P	P	20011128 <--		
US	2001-334301P	P	20011128 <--		
US	2002-387292P	P	20020607 <--		
US	2002-391777P	P	20020625 <--		
US	2002-396594P	P	20020717 <--		
US	2002-404249P	P	20020816 <--		
US	2002-407527P	P	20020828 <--		
WO	2003-US31974	W	20031008		

AB The invention includes methods and compns. for remodeling a peptide mol., including the addition or deletion of one or more glycosyl groups to a peptide, and/or the addition of a modifying group to a peptide. Methods of modifying the structure and properties of **erythropoietin** by introduction of glycosidation are described. The method uses substitution variants of **erythropoietin** to introduce sites that can be **glycosylated** enzymically. The primary **glycosylation** may then be used to add further sugar residues. The glycosidation, which may include the introduction of N-acetylglucose, N-acetylgalactose, and sialic acid and mannosyl and fucosyl oligosaccharides. The carbohydrate moiety may in turn be modified by **PEGylation.** A biantennary glycosidated derivative of Epogen had 146% of the activity of the unmodified protein. The **glycosylated** proteins had longer serum half-lives than the unmodified protein and showed longer term effects on blood Hb levels.

IT **681860-67-3DP**, substitution derivs., **glycosylated**, **PEGylated**
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; **erythropoietin glycosylation** and modification of protein structure and activity for therapeutic use)

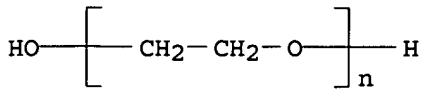
RN 681860-67-3 HCAPLUS
CN Erythropoietin (human 165-amino acid isoform) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **11096-26-7DP**, **Erythropoietin**, **glycosylated** derivs. **25322-68-3DP**, **Polyethylene glycol**, reaction products with **glycosylated erythropoietin**
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**erythropoietin glycosylation** and modification of protein structure and activity for therapeutic use)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



IT **113427-24-0DP**, Epogen, **glycosylated** derivs.
RL: PKT (Pharmacokinetics); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)
(preparation and pharmacokinetics of; **erythropoietin glycosylation** and modification of protein structure and activity for therapeutic use)
RN 113427-24-0 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:287861 HCAPLUS
DN 140:320038
TI Chimeric and humanized anti-granulocyte antibodies, **immunoconjugates** and labeled antibodies for diagnosis and treatment of malignancy, infection and inflammation
IN Goldenberg, David M.; Hansen, Hans; Leung, Shui-on
PA Immunomedics, Inc., USA; Mccall, John Douglas
SO PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004029093	A2	20040408	WO 2003-GB4229	20030930 <--
WO 2004029093	A3	20040603		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CN 1542019	A	20041103	CN 2003-123054	20030429 <--
CA 2500250	AA	20040408	CA 2003-2500250	20030930 <--
EP 1546204	A2	20050629	EP 2003-751001	20030930 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI US 2002-414341P	P	20020930 <--		
WO 2003-GB4229	W	20030930		

AB The present invention provides humanized, chimeric and human MN3 antibodies, fusion proteins, and fragments that bind NCA90 and NCA95 antigens. The antibodies, fusion proteins, and fragments thereof, as well

as combinations with other suitable antibodies, are useful for the treatment and diagnosis of granulocyte related disorders and diseases, such as leukemia.

IT **11096-26-7**, **Erythropoietin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chimeric and humanized anti-granulocyte antibodies, **immunoconjugates** and labeled antibodies for diagnosis and treatment of malignancy, infection and inflammation)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **7439-89-6**, **Iron**, biological studies **15438-31-0**
, **Iron**(2+), biological studies **20074-52-6**,
Iron(3+), biological studies
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chimeric and humanized anti-granulocyte antibodies, **immunoconjugates** and labeled antibodies for diagnosis and treatment of malignancy, infection and inflammation)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

RN 15438-31-0 HCAPLUS
CN Iron, ion (Fe2+) (8CI, 9CI) (CA INDEX NAME)

Fe^{2+}

RN 20074-52-6 HCAPLUS
CN Iron, ion (Fe3+) (8CI, 9CI) (CA INDEX NAME)

Fe^{3+}

L108 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:203692** HCAPLUS
DN **140:229921**
TI Use of **erythropoietin** and analogs to treat disturbances of iron distribution in diabetes
IN Lehmann, Paul; Roeddiger, Ralf; Walter-Matsui, Ruth
PA F. Hoffmann-La Roche A.-G., Switz.
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004019972	A1	20040311	WO 2003-EP9194	20030820 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004110679 A1 20040610 US 2003-634477 20030804 <--
CA 2496581 AA 20040311 CA 2003-2496581 20030820 <--
EP 1536823 A1 20050608 EP 2003-790911 20030820 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
BR 2003013792 A 20050712 BR 2003-13792 20030820 <--
PRAI EP 2002-19100 A 20020829 <--
WO 2003-EP9194 W 20030820

AB The present invention relates to the use of **erythropoietin** for the treatment of disturbances of iron distribution in diabetes.

IT **668496-68-2 668496-69-3**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; use of **erythropoietin** (**Epo**) and analogs to treat disturbances of iron distribution in diabetes)

RN 668496-68-2 HCAPLUS
CN Erythropoietin (human 165-amino acids variant) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 668496-69-3 HCAPLUS
CN Erythropoietin (human 166-amino acids variant) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **11096-26-7, Erythropoietin 11096-26-7D, Erythropoietin, glycosylated** and **PEGylated** variants and **conjugates**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **erythropoietin** (**Epo**) and analogs to treat disturbances of iron distribution in diabetes)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **113427-24-0, Epoetin alfa 122312-54-3, Epoetin beta 209810-58-2, Darbepoetin alfa**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **erythropoietin** (**Epo**) and analogs to treat disturbances of iron distribution in diabetes)

RN 113427-24-0 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 122312-54-3 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety),

glycoform β (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 209810-58-2 HCAPLUS
CN Erythropoietin [30-asparagine,32-threonine,87-valine,88-asparagine,90-threonine] (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Harold, T	2002			US 6440932 B1	HCAPLUS
Hoffmann La Roche	2001			WO 0187329 A	HCAPLUS
Hoffmann La Roche	2003			WO 03025583 A	HCAPLUS

L108 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:282607** HCAPLUS
DN **138:298131**
TI **PEGylated** and **diglycosylated erythropoietin** with improved pharmaceutical properties in induction of erythropoiesis
IN Tischer, Wilhelm
PA F. Hoffmann-La Roche Ag, Switz.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2003029291	A2	20030410	WO 2002-EP10556	20020920	<--
	WO 2003029291	A3	20030724			
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW					
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	US 2003077753	A1	20030424	US 2002-241356	20020911	<--
	US 6930086	B2	20050816			
	CA 2460489	AA	20030410	CA 2002-2460489	20020920	<--
	EP 1432802	A2	20040630	EP 2002-777160	20020920	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
	CN 1558952	A	20041229	CN 2002-818752	20020920	<--
	JP 2005509609	T2	20050414	JP 2003-532536	20020920	<--
PRAI	EP 2001-122555	A	20010925	<--		
	WO 2002-EP10556	W	20020920	<--		

AB The invention provides a new class of **EPO** muteins with improved pharmaceutical properties. The **EPO** muteins according to the invention have the in vivo biol. activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The invention provides an **erythropoietin** mutein which has retained the potential N-**glycosylation** sites at Asn24, Asn38, Asn83, is N-**glycosylated** at Asn38 and Asn83 but is not N-**glycosylated** at Asn24 and is preferably linked at the N-terminal amino group and/or the

ε-amino group of Lys20 to **poly(ethylene glycol)** group(s) (**PEG**), preferably to alkoxypoly(ethylene glycol) group(s), more preferably to lower methoxypoly(ethylene glycol) group(s). The muteins of this invention have the same uses as **EPO**. In particular, the muteins of this invention are useful to treat patients by stimulating the division and differentiation of committed erythroid progenitors in the bone marrow. The present invention also includes a method for the treatment of anemia in humans and the use of the muteins for the manufacturing of a pharmaceutical agent preferably for such treatment. The present invention also includes a method for preparing **erythropoietin** muteins according to the invention, which comprises the production of a **glycosylated EPO** fragment consisting of the amino acids 26-165-(**EPO** 26-165) and subsequent fusion of said fragment with a **nonglycosylated** but preferably **PEGylated EPO** fragment consisting of the amino acids 1-28 (**EPO** 1-28).

IT **510776-46-2DP**, muteins **510776-47-3DP**, muteins
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; preparation of **PEGylated** and **diglycosylated erythropoietin** with improved pharmaceutical properties in induction of erythropoiesis)
RN 510776-46-2 HCAPLUS
CN Erythropoietin (human 165-amino acid isoform) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 510776-47-3 HCAPLUS
CN Erythropoietin (human 166-amino acid isoform) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **510776-48-4**, 29-165-**erythropoietin** (human)
RL: RCT (Reactant); RACT (Reactant or reagent)
(amino acid sequence; preparation of **PEGylated** and **diglycosylated erythropoietin** with improved pharmaceutical properties in induction of erythropoiesis)
RN 510776-48-4 HCAPLUS
CN 29-165-erythropoietin (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **11096-26-7DP**, **Erythropoietin**, muteins
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **PEGylated** and **diglycosylated erythropoietin** with improved pharmaceutical properties in induction of erythropoiesis)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:869575** HCAPLUS
DN **137:346941**
TI Method for improving the quality of life of patients by administration of **erythropoietin** (**RhuEPO**)
IN Zaharia, Veronica C.
PA USA
SO U.S. Pat. Appl. Publ., 4 pp., Cont.-in-part of U.S. Ser. No. 872,630.

CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002169129	A1	20021114	US 2002-133545	20020426 <--
	US 5951996	A	19990914	US 1998-18815	19980204 <--
	US 6274158	B1	20010814	US 1999-335076	19990617 <--
	US 6521245	B1	20030218	US 2001-872630	20010601 <--
PRAI	US 1998-18815	A2	19980204 <--		
	US 1998-91598P	P	19980702 <--		
	US 1999-125253P	P	19990319 <--		
	US 1999-335076	A3	19990617 <--		
	US 2001-287206P	P	20010428 <--		
	US 2001-872630	A2	20010601 <--		

AB A method for providing various benefits with the administration of different quantities of **Erythropoietin.** The method provides for enhancing the of quality of life by administration of **Erythropoietin** before a substantial increases in Hb occurs. The improvement in quality of life is independent of the hemopoietic effect. In larger quantities the administration of **RhuEPO** leads to repair of vascular damage and leads to the redistribution of the **iron** trapped in storage organs, from where it cannot be used for red blood cell production, into the hemopoietic system leading to enhanced red blood cell production

IT **11096-26-7**, **Erythropoietin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for improving the quality of life of patients by administration of **erythropoietin** (**RhuEPO**))
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **7439-89-6**, **Iron**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method for limiting chronic blood loss by administering **RhuEPO** to prevent **iron** loss and to increase Hb level, increased mean corpuscular Hb, and increased red blood cell hemoglobinization.)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

L108 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:785122** HCAPLUS
DN **138:298038**
TI Long-term reversal of chronic anemia using a hypoxia-regulated **erythropoietin** gene therapy
AU Binley, Katie; Askham, Zoe; Iqball, Sharifah; Spearman, Hayley; Martin, Leigh; de Alwis, Mahesh; Thrasher, Adrian J.; Ali, Robin R.; Maxwell, Patrick H.; Kingsman, Susan; Naylor, Stuart
CS Oxford BioMedica (UK) Ltd, London, OX4 4GA, UK
SO Blood (**2002**), 100(7), 2406-2413
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology

DT Journal
LA English
AB Anemia is a common clin. problem, and there is much interest in its role in promoting left ventricular hypertrophy through increasing cardiac workload. Normally, red blood cell production is adjusted through the regulation of **erythropoietin** (**Epo**) production by the kidney. One important cause of anemia is relative deficiency of **Epo**, which occurs in most types of renal disease. Clin., this can be corrected by supplementation with recombinant **Epo**. Here the authors describe an oxygen-regulated gene therapy approach to treating homozygous **erythropoietin**-SV40 T antigen (**Epo**-TAgh) mice with relative **erythropoietin** deficiency. The authors used vectors in which murine **Epo** expression was directed by an Oxford Biomedica hypoxia response element (OBHRE) or a constitutive cytomegalovirus (CMV) promoter. Both corrected anemia, but CMV-**Epo** -treated mice acquired fatal polycythemia. In contrast, OBHRE-**Epo** corrected the hematocrit level in anemic mice to a normal physiol. level that stabilized without resulting in polycythemia. Importantly, the OBHRE-**Epo** vector had no significant effect on the hematocrit of control mice. Homozygous **Epo**-TAgh mice display cardiac hypertrophy, a common adaptive response in patients with chronic anemia. In the OBHRE-**Epo**-treated **Epo**-TAgh mice, the authors observed a significant reversal of cardiac hypertrophy. The authors conclude that the OBHRE promoter gives rise to physiol. regulated **Epo** secretion such that the hematocrit level is corrected to healthy in anemic **Epo**-TAgh mice. This establishes that a hypoxia regulatory mechanism similar to the natural mechanism can be achieved, and it makes **EPO** gene therapy more attractive and safer in clin. settings. The authors envisage that this control system will allow regulated delivery of therapeutic gene products in other ischemic settings.
IT **7439-89-6**, **Iron**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(long-term reversal of chronic anemia using hypoxia-regulated **erythropoietin** gene therapy)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

IT **11096-26-7**, **Erythropoietin**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-term reversal of chronic anemia using hypoxia-regulated **erythropoietin** gene therapy)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1989	2	20	Lancet	
Bachmann, S	1993	41	335	J Histochem Cytochem	HCAPLUS
Bartholomew, A	2001	12	1527	Hum Gene Ther	HCAPLUS
Beall, C	2000	7	534	Gene Ther	HCAPLUS
Binley, K	1999	6	1721	Gene Ther	HCAPLUS
Boast, K	1999	10	2197	Hum Gene Ther	HCAPLUS

Bohl, D	1998	92	1512	Blood	HCAPLUS
Bohl, D	2000	95	2793	Blood	HCAPLUS
Bohl, D	1997	3	299	Nat Med	HCAPLUS
Bron, D	2001	28	1	Semin Oncol	MEDLINE
Cowgill, L	1998	212	521	J Am Vet Med Assoc	HCAPLUS
Dalle, B	1999	6	157	Gene Ther	HCAPLUS
Erslev, A	1985	41	213	Nephron	MEDLINE
Eschbach, J	1989	35	134	Kidney Int	MEDLINE
Foley, R	1995	5	2024	J Am Soc Nephrol	MEDLINE
Goodnough, L	2000	96	823	Blood	HCAPLUS
Griffiths, L	2000	7	255	Gene Ther	HCAPLUS
Hamamori, Y	1995	95	1808	J Clin Invest	HCAPLUS
Jelkmann, W	1992	72	449	Physiol Rev	HCAPLUS
Kina, T	2000	109	280	Br J Haematol	HCAPLUS
Krystal, G	1983	11	649	Exp Hematol	HCAPLUS
Lynch, C	1999	1	493	Curr Opin Mol Ther	HCAPLUS
Maxwell, P	1993	44	1149	Kidney Int	HCAPLUS
Maxwell, P	1993	90	2423	Proc Natl Acad Sci U	HCAPLUS
Middleton, R	2001	12	1079	J Am Soc Nephrol	MEDLINE
Post, D		8	1801	Gene Ther	HCAPLUS
Raja, K	1997	96	248	Br J Haematol	HCAPLUS
Rendahl, K	1998	16	757	Nat Biotechnol	HCAPLUS
Rinsch, C	1997	8	1881	Hum Gene Ther	HCAPLUS
Rudich, S	2000	90	102	J Surg Res	HCAPLUS
Semenza, G	2000	14	1983	Genes Dev	HCAPLUS
Seppen, J	2001	98	594	Blood	HCAPLUS
Serguera, C	1999	10	375	Hum Gene Ther	HCAPLUS
Setoguch, Y	1994	84	2946	Blood	
Villeval, J	1994	84	928	Blood	HCAPLUS
Wang, G	1993	90	4304	Proc Natl Acad Sci U	HCAPLUS
Wang, G	1995	92	5510	Proc Natl Acad Sci U	HCAPLUS
Ye, X	1999	283	88	Science	HCAPLUS
Zhang, X	1999	10	2527	Hum Gene Ther	HCAPLUS
Zhou, S	1998	5	665	Gene Ther	HCAPLUS

L108 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:761224** HCAPLUS
DN **137:288375**
TI The correction of anemia in severe resistant heart failure with **erythropoietin** and intravenous **iron** prevents the progression of both the heart and the renal failure and markedly reduces hospitalization
AU Silverberg, D. S.; Wexler, D.; Blum, M.; Tchebiner, J.; Sheps, D.; Keren, G.; Schwartz, D.; Baruch, R.; Yachnin, T.; Shaked, M.; Zubkov, A.; Steinbruch, S.; Iaina, A.
CS Department of Nephrology and Cardiology and Congestive Heart Failure Unit and Medical Department B, Tel Aviv Medical Center, Tel Aviv-Jaffa, 64239, Israel
SO Clinical Nephrology (**2002**), 58(1, Suppl. 1), S37-S45
CODEN: CLNHBI; ISSN: 0301-0430
PB Dustri-Verlag Dr. Karl Feistle
DT Journal; General Review
LA English
AB A review. Both Congestive Heart Failure (CHF) and Chronic Renal Failure (CRF) are increasing steadily in the community. We propose that there is a vicious circle established whereby CHF and CRF both cause anemia and the anemia then worsens both the CHF and CRF causing more anemia and so on. We call this the Cardio Renal Anemia (CRA) syndrome. By the combination of active treatment of the CHF and control of the anemia with s.c. **erythropoietin** and i.v. **iron**, the progression of both

the CHF and the CRF can be slowed or stopped in most cases, the quality of life improved and the need for recurrent hospitalization reduced. This will involve cooperation between internists, cardiologists, and nephrologists to allow early and maximal therapy of both the CHF and the anemia.

IT **7439-89-6**, **Iron**, biological studies **11096-26-7**
, **Erythropoietin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**erythropoietin** and i.v. **iron** correction of anemia in severe resistant heart failure patients prevents progression of both heart and renal failure and markedly reduces hospitalization)

RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Al-Ahmad, A	2001	38	955	J Am Coll Cardiol	MEDLINE
Anand, I	1993	70	357	Br Heart J	MEDLINE
Bosman, D	2001	24	495	Diabetes Care	MEDLINE
Capes, S	2000	23	377	Diabetes Care	HCAPLUS
Carson, J	1995	170	32S	Amer J Surg	
Cowie, M	1997	18	208	Eur Heart J	HCAPLUS
Dries, D	2001	38	421	J Am Coll Cardiology	MEDLINE
Felker, G	2001	17		Circulation	
Fine, L	1998	53	s74	Kidney Int	
Fine, L	2000	57	S22	Kidney Int	
Fishbane, S	1995	26	41	Am J Kidney Dis	MEDLINE
Foley, R	1996	28	53	Am J Kidney Dis	MEDLINE
Foley, R	1995	47	186	Kidney Int	MEDLINE
Goodnough, L	2001	345	1272	N Engl J Med	MEDLINE
Hampl, H	1985	39	102	Nephron	MEDLINE
He, J	2001	161	996	Arch Int Med	MEDLINE
Herrera-Garza, E	1999	115	1170	Chest	MEDLINE
Hillege, H	1999	10	A384	J Am Soc Nephrol	
Holland, D	2000	15	650	Nephrol Dial Transpl	MEDLINE
Iverson, P	2002	282	R166	Am J Physiol Regul I	
Jafar, T	2001	60	1131	Kidney Int	HCAPLUS
Johnson, D	1996	5	186	Current Opinion in N	MEDLINE
Jungers, P	2001	16	307	Nephrol Dialysis Tra	HCAPLUS
Katz, A	1994	121	363	Ann Intern Med	HCAPLUS
Knight, E	1999	138	849	Am Ht J	MEDLINE
Kratz, A	1998	339	1063	N Engl J Med	MEDLINE
Kuriyama, S	1997	77	176	Nephron	HCAPLUS
Linde, T	1996	30	115	Scand J Urol Nephrol	MEDLINE
Longenecker, J	2000	11	520	J Am Soc Nephrol	MEDLINE
Macdougall, I	1996	50	1694	Kidney Int	HCAPLUS
Macdougall, I	1999	14	1836	Nephrol Dial Transpl	MEDLINE
Major, A	1997	98	292	Brit J Haematol	HCAPLUS
Mancini, D	2000	101	1080	Circulation	MEDLINE

Mancini, D	2001	17		Circulation	
McAlister, F	1999	138	87	Amer Heart J	MEDLINE
Means, R	1999	70	7	Int J Hematol	
Miller, L	2001	19	547	Cardiology Clinics	MEDLINE
Mosterd, A	2001	22	1318	Eur Heart J	MEDLINE
O'Connell, J	2000	23	6	Clin Cardiol	
Packer, M	1999	83	1	Am J Cardiol	
Perry, H	1995	25	587	Hypertension	
Petrie, M	2001	22	1978	Eur Heart J	MEDLINE
Philbin, E	2000	109	605	Amer J Med	HCAPLUS
Rich, M	1995	333	1190	N Engl J Med	MEDLINE
Roth, D	1994	24	777	Am J Kidney Dis	MEDLINE
Silagy, C	1993	54	84	Clin Pharm Therapy	MEDLINE
Silverberg, D	2001	23	1	Clin Lab Haem	MEDLINE
Silverberg, D	2000	35	1737	J Am Coll Cardiol	HCAPLUS
Silverberg, D	2001	37	1775	J Am Coll Cardiol	HCAPLUS
Silverberg, D	1996	72	413	Nephron	HCAPLUS
Silverberg, D	2001	21	S236	Periton Dial Int	
Sommerburg, O	2000	53	S23	Clin Nephrol	
Sunder-Plassmann, G	2001	38	S20	Am J Kidney Diseases	
Tong, E	2001	21	190	Seminars in Nephrolo	HCAPLUS
Tsuyuki, R	2001	161	2337	Archives Int Med	MEDLINE
US Renal Data System	2001			Annual Data Report	
Vaziri, N	2001	38	1	Am J Kidney Dis	HCAPLUS
Wahr, J	1998	81	10	Br J Anaest	
Winkler, A	1999	16	813	Diabetes Medicine	MEDLINE
Wisniacki, N	2001	85	P4	Heart	
Wu, W	2001	345	1230	N Engl J Med	MEDLINE
Yoshida, H	1998	53	880	Kidney Int	MEDLINE

L108 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:487418** HCAPLUS
DN **137:68127**
TI **Erythropoietin conjugates**
IN Burg, Josef; Engel, Alfred; Franze, Reinhard; Hilger, Bernd; Schurig, Hartmut Ernst; Tischer, Wilhelm; Wozny, Manfred
PA F. Hoffmann-La Roche Ag, Switz.
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002049673	A2	20020627	WO 2001-EP14434	20011208 <--
WO 2002049673	A3	20030123		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2431964	AA	20020627	CA 2001-2431964	20011208 <--
AU 2002033230	A5	20020701	AU 2002-33230	20011208 <--
EP 1345628	A2	20030924	EP 2001-984811	20011208 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

BR 2001016381	A	20040225	BR 2001-16381	20011208	<--
JP 2004525097	T2	20040819	JP 2002-551010	20011208	<--
CN 1527726	A	20040908	CN 2001-820609	20011208	<--
US 2002115833	A1	20020822	US 2001-14363	20011211	<--
ZA 2003004647	A	20040913	ZA 2003-4647	20030613	<--
PRAI EP 2000-127891	A	20001220	<--		
WO 2001-EP14434	W	20011208	<--		

AB The present invention refers to **conjugates** of **erythropoietin** with **poly(ethylene glycol)** comprising an **erythropoietin** glycoprotein having an N-terminal α-amino group and having the in vivo biol. activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and selected from the group consisting of human **erythropoietin** and analogs thereof which have the sequence of human **erythropoietin** modified by the addition of from 1 to 6 **glycosylation** sites or a rearrangement of at least one **glycosylation** site; said glycoprotein being covalently linked to one **poly(ethylene glycol)** group of the formula -CO-(CH2)x-(OCH2CH2)m-OR with the -CO of the **poly(ethylene glycol)** group forming an amide bond with said N-terminal α-amino group; wherein R is lower alkyl; x is 2 or 3; and m is from about 450 to about 1350.

IT **11096-26-7DP, Erythropoietin, conjugates**
RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**glycosylation** site-augmented human **erythropoietin** **conjugates** with **PEG**)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

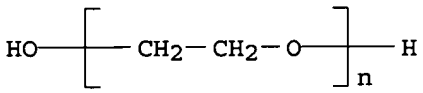
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **11096-26-7, Erythropoietin 25322-68-3D, Polyethylene glycol, erythropoietin conjugates**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**glycosylation** site-augmented human **erythropoietin** **conjugates** with **PEG**)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L108 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:409245** HCAPLUS
DN **136:380106**
TI Method of treating congestive heart failure with **erythropoietin** and an **iron** compound
IN Iaina, Adrian; Wexler, Dov; Silverberg, Donald S.
PA Israel
SO U.S. Pat. Appl. Publ., 3 pp.

CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002065214	A1	20020530	US 2000-725161	20001129 <--
PRAI US 2000-725161		20001129 <--		

AB A method of treating congestive heart failure in a subject suffering therefrom, comprising administering **erythropoietin** and i.v. administering an i.v. administrable **iron** compound to the subject. The **iron** is preferably administered in the form of a complex of a ferric hydroxide with **erythropoietin.**
IT **11096-26-7, Erythropoietin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating congestive heart failure with **erythropoietin** and an **iron** compound)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:850963** HCAPLUS
DN **136:11065**
TI New pharmaceutical composition
IN Papadimitriou, Apollon
PA F. Hoffmann-La Roche A.-G., Switz.
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001087329	A1	20011122	WO 2001-EP5187	20010508 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CU, CZ, DE, DK, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2408685	AA	20011122	CA 2001-2408685	20010508 <--
BR 2001010914	A	20030211	BR 2001-10914	20010508 <--
EP 1311285	A2	20030521	EP 2001-943331	20010508 <--
EP 1311285	B1	20050323		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003533487	T2	20031111	JP 2001-583796	20010508 <--
NZ 522030	A	20041126	NZ 2001-522030	20010508 <--
AT 291436	E	20050415	AT 2001-943331	20010508 <--
EP 1525889	A1	20050427	EP 2005-984	20010508 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR				
US 2002037841	A1	20020328	US 2001-853731	20010511 <--
ZA 2002008500	A	20040128	ZA 2002-8500	20021021 <--

NO 2002005450 A 20021114 NO 2002-5450 20021114 <--
US 2004147431 A1 20040729 US 2004-780297 20040217 <--
PRAI EP 2000-110355 A 20000515 <--
EP 2001-943331 A3 20010508 <--
WO 2001-EP5187 W 20010508 <--
US 2001-853731 A1 20010511 <--

AB The present invention relates to a liquid pharmaceutical composition comprising an **erythropoietin** protein, a multiple charged inorg. anion in a pharmaceutically acceptable buffer suitable to keep the solution pH in the range from about 5.5 to about 7.0, and optionally one or more pharmaceutically acceptable excipients. This composition is especially useful for the prophylaxis and treatment of diseases related to erythropoiesis.

IT **96024-34-9P**, **Erythropoietin** (human clone λHEPOFL13 protein moiety reduced) **134547-95-8P**, 1-165-**Erythropoietin** (human clone λHEPOFL13 protein moiety reduced)
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; stabilized **erythropoietin** pharmaceutical composition)

RN 96024-34-9 HCAPLUS
CN Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 134547-95-8 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

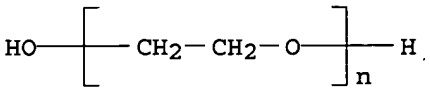
IT **11096-26-7P**, **Erythropoietin**
RL: BPN (Biosynthetic preparation); PEP (Physical, engineering or chemical process); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(stabilized **erythropoietin** pharmaceutical composition)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **25322-68-3D**, **Polyethylene glycol**, protein **conjugates**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stabilized **erythropoietin** pharmaceutical composition)

RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File

Alkermes	1996			WO 9640073 A	HCAPLUS
Chugai Seiyaku Kk	1986			EP 0178665 A	HCAPLUS
Chugai Seiyaku Kk	1986			GB 2171304 A	HCAPLUS
Chugai Seiyaku Kk	1999			EP 0909564 A	HCAPLUS
Woog, H	1991			US 4992419 A	HCAPLUS

L108 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:715798** HCAPLUS
DN **136:15603**
TI **Erythropoietin** therapy and preoperative autologous blood donation in children undergoing open heart surgery
AU Sonzogni, V.; Crupi, G.; Poma, R.; Annechino, F.; Ferri, F.; Filisetti, P.; Bellavita, P.
CS Department of Anesthesiology, Ospedali Riuniti di Bergamo, Bergamo, Italy
SO British Journal of Anaesthesia (**2001**), 87(3), 429-434
CODEN: BJANAD; ISSN: 0007-0912
PB Oxford University Press
DT Journal
LA English
AB We assessed the feasibility and efficacy of s.c. **erythropoietin** alpha (**EPO**) therapy and preoperative autologous blood donation (ABD) in children undergoing open heart surgery. Thirty-nine children were treated consecutively with **EPO** (100 U kg-1 s.c. three times a week in the 3 wk preceding the operation and i.v. on the day of surgery) and two ABDs were made (Group 1). As controls to compare transfusion requirements, 39 consecutive age-matched patients who had undergone open heart surgery during the two preceding years were selected (Group 2). In a mean time of 20 (SD 5) days, 96% of scheduled ABDs were performed and only three mild vasovagal reactions were observed The mean volume of autologous red blood cells (RBC) collected was 6 (1) ml kg-1 and the mean volume of autologous RBC produced as a result of **EPO** therapy before surgery was 7 (3) ml kg-1, corresponding to a 28 (11)% increase in circulating RBC volume The mean volume of autologous RBC collected was not different from that produced [6 (1) vs. 7 (3) ml kg-1, P=0.4]. Allogenic blood was administered to three out of 39 children in Group 1 (7.7%) and to 24 out of 39 (61.5%) in Group 2. Treatment with s.c. **EPO** increases the amount of autologous blood that can be collected and minimizes allogenic blood exposure in children undergoing open heart surgery.
IT **113427-24-0, Eprex**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**erythropoietin** therapy and preoperative autologous blood donation in children undergoing open heart surgery)
RN 113427-24-0 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adamson, J	1994	115	7	Surgery	MEDLINE
Anon	1988	260	2700	Consensus conference	
Baron, J	1997	33	64	Semin Hematol	
Beguin, Y	1999	84	541	Haematologica	HCAPLUS
Chaplin, H	1953	32	1309	J Clin Invest	
Cooley, D	1995	170	53	Am J Surg	
Coyle, D	2000	18	161	Pharmacoeconomics	MEDLINE

Despotis, G	1999	11	84	Semin Thorac Cardiov	MEDLINE
Fukahara, K	1997	114	504	J Thoroc Cardiovasc	MEDLINE
Goodnough, L	1994	101	354	Am J Clin Pathol	MEDLINE
Goodnough, L	1995	60	473	Ann Thorac Surg	MEDLINE
Goodnough, L	1990	115	28	J Lab Clin Med	MEDLINE
Goodnough, L	1989	321	1163	N Engl J Med	MEDLINE
Goodnough, L	1997	336	933	N Engl J Med	MEDLINE
Goodnough, L	1999	340	438	N Engl J Med	MEDLINE
Goodnough, L	1992	32	441	Transfusion	MEDLINE
Goodnough, L	1993	33	944	Transfusion	MEDLINE
Goodnough, L	1994	34	66	Transfusion	MEDLINE
Guay, J	1996	62	1955	Ann Thorac Surg	MEDLINE
Klapper, E	1995	110	1594	J Thorac Cardiovasc	MEDLINE
Krantz, S	1991	77	419	Blood	HCAPLUS
Marchetti, M	2000	40	673	Transfusion	MEDLINE
Masuda, M	1995	60	1694	Ann Thorac Surg	MEDLINE
Mayer, M	1996	70	224	Vax Sang	MEDLINE
McVay, P	1990	30	249	Transfusion	MEDLINE
Mercuriali, F	1993	30	17	Semin Hematol	
Price, T	1996	36	29	Transfusion	MEDLINE
Robertie, P	1990	28	197	Int Anaesthesiol Cli	MEDLINE
Russell, S	1949	24	88	Arch Dis Child	
Schmoeckel, M	1993	41	363	Thorac Cardiovasc Su	
Shaddy, R	1995	149	322	Arch Pediatr Adolesc	MEDLINE
Shimpo, H	1997	111	1565	Chest	HCAPLUS
Sowade, O	1997	89	411	Blood	HCAPLUS
Tasaki, T	1994	66	188	Vax Sang	MEDLINE
Walpoth, B	1997	33	75	Semin Hematol	
Watanabe, Y	1992	54	479	Ann Thorac Surg	MEDLINE
Welch, H	1992	116	393	Ann Intern Med	MEDLINE
Williams, G	1999	89	57	Anesth Analg	MEDLINE

L108 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:505221** HCAPLUS
DN **135:267638**
TI The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous **erythropoietin** and intravenous **iron**: a randomized controlled study
AU Silverberg, Donald S.; Wexler, Dov; Sheps, David; Blum, Miriam; Keren, Gad; Baruch, Ron; Schwartz, Doron; Yachnin, Tatyana; Steinbruch, Shoshana; Shapira, Itzhak; Laniado, Shlomo; Iaina, Adrian
CS Department of Nephrology and Cardiology and Congestive Heart Failure, Tel Aviv Medical Center, Tel Aviv-Jaffa, Israel
SO Journal of the American College of Cardiology (**2001**), 37(7), 1775-1780
CODEN: JACCDI; ISSN: 0735-1097
PB Elsevier Science Inc.
DT Journal
LA English
AB This is a randomized controlled study of anemic patients with severe congestive heart failure (CHF) to assess the effect of correction of the anemia on cardiac and renal function and hospitalization. Although mild anemia occurs frequently in patients with CHF, there is very little information about the effect of correcting it with **erythropoietin** (**EPO**) and i.v. **iron**. Thirty-two patients with moderate to severe CHF (New York Heart Association [NYHA] class III to IV) who had a left ventricular ejection fraction (LVEF) of ≤40% despite maximally tolerated doses of CHF medications and whose Hb levels were persistently between 10.0 and 11.5 g% were randomized into two groups. Group A (16 patients) received s.c. **EPO** and IV **iron** to

increase the level of Hb to at least 12.5 g%. In Group B (16 patients) the anemia was not treated. The doses of all the CHF medications were maintained at the maximally tolerated levels except for oral and i.v. (IV) furosemide, whose doses were increased or decreased according to the clin. need. Over a mean of 8.2±2.6 mo, four patients in Group B and none in Group A died of CHF-related illnesses. The mean NYHA class improved by 42.1% in A and worsened by 11.4% in B. The LVEF increased by 5.5% in A and decreased by 5.4% in B. The serum creatinine did not change in A and increased by 28.6% in B. The need for oral and IV furosemide decreased by 51.3% and 91.3% resp. in A and increased by 28.5% and 28.0% resp. in B. The number of days spent in hospital compared with the same period of time before entering the study decreased by 79.0% in A and increased by 57.6% in B. When anemia in CHF is treated with **EPO** and IV **iron**, a marked improvement in cardiac and patient function is seen, associated with less hospitalization and renal impairment and less need for diuretics.

IT **11096-26-7**, **Erythropoietin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of correction of mild anemia in congestive heart failure using s.c. **erythropoietin** and i.v. **iron**)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Al-Ahmad, A	2000	11	137A	J Am Soc Nephrol	
Alexander, M	1999	137	919	Am Heart J	MEDLINE
Ali, A	1999	138	1133	Am Heart J	MEDLINE
Anand, I	1993	70	357	Br Heart J	MEDLINE
Anon	1997	30	S193	Am J Kidney Dis	
Bardaji, A	1998	32	970	Am J Kid Dis	MEDLINE
Carson, J	1995	170	32	Am J Surg	
Carson, J	1996	348	1055	Lancet	MEDLINE
De Simone, G	2000	101	152	Circulation	MEDLINE
Fine, L	1998	53	S74	Kidney Intl	
Fishbane, S	1995	26	41	Am J Kidney Dis	MEDLINE
Foley, R	1996	28	53	Am J Kidney Dis	MEDLINE
Ghali, J	1988	148	2013	Arch Intern Med	MEDLINE
Goldberg, N	1992	124	424	Am Heart J	MEDLINE
Haber, H	1991	324	353	N Engl J Med	MEDLINE
Harnett, J	1995	47	884	Kidney Int	MEDLINE
Hebert, P	1997	155	1618	Am J Respir Crit Car	MEDLINE
Hillege, H	1999	10	A384	J Am Soc Nephrol	
Jensen, J	1993	233	125	J Int Med	MEDLINE
Kannel, W	1987	8	23	Eur Heart J	
Knight, E	1999	138	849	Am Heart J	MEDLINE
Kuriyama, S	1996	9	426	Am J Hypertension	HCAPLUS
Locatelli, F	1998	13	1642	Nephrol Dial Transpl	MEDLINE
Low-Friedrich, I	1991	11	54	Am J Nephrol	MEDLINE
Ma, J	1999	10	610	J Am Soc Nephrol	MEDLINE
Macdougall, I	1996	50	1694	Kidney Int	HCAPLUS
Magri, P	1998	98	2849	Circulation	HCAPLUS
Maschio, G	1995	10	74	Nephrol Dial Transpl	
Opasich, C	1996	78	354	Am J Cardiol	MEDLINE
Packer, M	1999	83	1	Am J Cardiol	

Perry, H	1995	25	587	Hypertension	
Rich, M	1996	44	638	J Am Geriatr Soc	MEDLINE
Silverberg, D	2000	35	1737	J Am Coll Cardiol	HCAPLUS
Silverberg, D	1999	55	S79	Kidney Int	
Silverberg, D	1996	72	413	Nephron	HCAPLUS
Sowade, O	1997	129	97	J Lab Clin Med	HCAPLUS
Stefanski, A	1996	50	1321	Kidney Int	MEDLINE
Wackers, F	1979	43	1159	Am J Cardiol	MEDLINE
Wald, M	1996	167	461	J Cell Physiol	HCAPLUS
Wald, M	1995	71	190	Nephron	HCAPLUS
Wu, H	1999	126	3597	Development	HCAPLUS
Xia, H	1999	10	1309	J Am Soc Nephrol	MEDLINE
Yoshida, H	1998	53	880	Kidney Int	MEDLINE

L108 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:31360** HCAPLUS
DN **134:105827**
TI **Erythropoietin** derivatives
IN Burg, Josef; Hilger, Bernd; Josel, Hans-Peter
PA F. Hoffmann-La Roche A.-G., Switz.
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001002017	A2	20010111	WO 2000-EP6009	20000628 <--
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2378533	AA	20010111	CA 2000-2378533	20000628 <--
	US 6340742	B1	20020122	US 2000-604871	20000628 <--
	EP 1196443	A2	20020417	EP 2000-951312	20000628 <--
	EP 1196443	B1	20040526		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 2000012138	A	20020507	BR 2000-12138	20000628 <--
	TR 200103782	T2	20020521	TR 2001-200103782	20000628 <--
	JP 2003503464	T2	20030128	JP 2001-507507	20000628 <--
	AU 768452	B2	20031211	AU 2000-64299	20000628 <--
	NZ 516170	A	20040227	NZ 2000-516170	20000628 <--
	AT 267840	E	20040615	AT 2000-951312	20000628 <--
	RU 2232163	C2	20040710	RU 2002-102232	20000628 <--
	PT 1196443	T	20040930	PT 2000-951312	20000628 <--
	ES 2220501	T3	20041216	ES 2000-951312	20000628 <--
	ZA 2001010097	A	20030307	ZA 2001-10097	20011207 <--
	NO 2001006304	A	20020219	NO 2001-6304	20011221 <--
PRAI	US 1999-142243P	P	19990702 <--		
	US 1999-147452P	P	19990805 <--		
	US 1999-151454P	P	19990830 <--		
	WO 2000-EP6009	W	20000628 <--		

AB **Erythropoietin** glycoprotein **conjugates** are disclosed, said **conjugates** comprise an **erythropoietin**

glycoprotein having at least one free amino group and having the in vivo biol. activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and selected from the group consisting of human **erythropoietin** and analogs thereof which have the primary structure of human **erythropoietin** modified by the addition of from 1 to 6 **glycosylation** sites or by the rearrangement of at least one **glycosylation** site; said glycoprotein being covalently linked to form one to three lower-alkoxy **poly(ethylene glycol)** groups, each **poly(ethylene glycol)** group being covalently linked to the glycoprotein via a linker of the formula -C(O)-X-S-Y- with the C(O) of the linker forming an amide bond with one of said amino groups, wherein X and Y are as defined in the description and claims, the average mol. weight of each **poly(ethylene glycol)** moiety is from about 20 kilodaltons to about 40 kilodaltons, and the mol. weight of the **conjugate** is from about 51 kilodaltons to about 175 kilodaltons.

IT **96024-34-9**, **Erythropoietin** (human clone λHEPOFL13 protein moiety reduced) **134547-95-8**, 1-165-**Erythropoietin** (human clone λHEPOFL13 protein moiety reduced)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(amino acid sequence; **erythropoietin** derivs. for increasing production of erythrocytes and reticulocytes)

RN 96024-34-9 HCAPLUS
CN Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 134547-95-8 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI) (CA INDEX NAME)

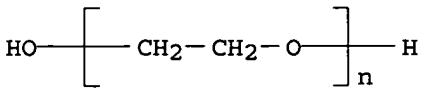
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **11096-26-7D**, **Erythropoietin, conjugates** **25322-68-3D**, **erythropoietin conjugates**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**erythropoietin** derivs. for increasing production of erythrocytes and reticulocytes)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L108 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:10610** HCAPLUS
DN **134:91083**

TI **Erythropoietin** derivatives for increasing bone marrow production of reticulocytes and erythrocytes
IN Bailon, Pascal Sebastian
PA F. Hoffmann-La Roche A.-G., Switz.
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 1064951	A2	20010103	EP 2000-113115	20000628	<--
	EP 1064951	A3	20020320			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
	US 6583272	B1	20030624	US 2000-604938	20000627	<--
	CA 2310536	AA	20010102	CA 2000-2310536	20000628	<--
	NO 2000003372	A	20010103	NO 2000-3372	20000628	<--
	TR 200001956	A2	20010122	TR 2000-200001956	20000628	<--
	HR 2000000436	A1	20010630	HR 2000-436	20000628	<--
	AU 736067	B2	20010726	AU 2000-42744	20000628	<--
	AU 2000042744	A5	20010104			
	NZ 505454	A	20011221	NZ 2000-505454	20000628	<--
	ZA 2000003282	A	20010102	ZA 2000-3282	20000629	<--
	CN 1280137	A	20010117	CN 2000-107889	20000629	<--
	SG 92717	A1	20021119	SG 2000-3658	20000629	<--
	DE 10031839	A1	20010201	DE 2000-10031839	20000630	<--
	GB 2353281	A1	20010221	GB 2000-16205	20000630	<--
	GB 2353281	B2	20040609			
	BG 104570	A	20010928	BG 2000-104570	20000630	<--
	IT 2000MI1479	A1	20011231	IT 2000-MI1479	20000630	<--
	IT 1318606	B1	20030827			
	ES 2191511	A1	20030901	ES 2000-1625	20000630	<--
	ES 2191511	B1	20050101			
	GB 2393960	A1	20040414	GB 2004-86	20000630	<--
	GB 2393960	B2	20040804			
	FR 2795734	A1	20010105	FR 2000-8609	20000703	<--
	JP 2001064300	A2	20010313	JP 2000-201525	20000703	<--
	BR 2000002276	A	20011211	BR 2000-2276	20000703	<--
	US 2003120045	A1	20030626	US 2002-293551	20021114	<--
	JP 2004155787	A2	20040603	JP 2003-419520	20031217	<--

PRAI	US 1999-142254P	P	19990702	<--
	US 1999-150225P	P	19990823	<--
	US 1999-151548P	P	19990831	<--
	US 1999-166151P	P	19991117	<--
	US 2000-604938	A1	20000627	<--
	GB 2000-16205	A3	20000630	<--
	JP 2000-201525	A3	20000703	<--

AB The present invention refers to **conjugates** of **erythropoietin** with **poly(ethylene glycol)** comprising an **erythropoietin** glycoprotein having at least one free amino group and having the in vivo biol. activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and selected from the group consisting of human **erythropoietin** and analogs thereof which have sequence of human **erythropoietin** modified by the addition of 1-6 **glycosylation** sites or a rearrangement of at least one **glycosylation** site; said glycoprotein being covalently linked to "n" **poly(ethylene glycol)** groups of the formula -CO-(CH2)x(OCH2CH2)m-OR with the carbonyl of each **poly(**

ethylene glycol) group forming an amide bond with one of said amino groups; wherein R is lower alkyl; x = 2 or 4; m = 450-900; n = 1-3; and n and m are chosen so that the mol. weight of the **conjugate** minus the **erythropoietin** glycoprotein is 20-100 kDa.

IT **134547-95-8P**, 1-165-**Erythropoietin** (human clone λHEPOFL13 protein moiety reduced)
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; **erythropoietin** derivs. for increasing bone marrow production of reticulocytes and erythrocytes)
RN 134547-95-8 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI) (CA INDEX NAME)

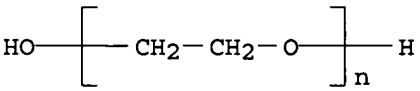
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **11096-26-7D**, **Erythropoietin**, **polyethylene glycol conjugates 221039-34-5**, **Erythropoietin** (human)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**erythropoietin** derivs. for increasing bone marrow production of reticulocytes and erythrocytes)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 221039-34-5 HCAPLUS
CN Erythropoietin (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **25322-68-3D**, **Polyethylene glycol**, glycoprotein **conjugates**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**erythropoietin** derivs. for increasing bone marrow production of reticulocytes and erythrocytes)
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



IT **96024-34-9**, **Erythropoietin** (human clone λHEPOFL13 protein moiety reduced)
RL: PRP (Properties)
(unclaimed protein sequence; **erythropoietin** derivs. for increasing bone marrow production of reticulocytes and erythrocytes)
RN 96024-34-9 HCAPLUS
CN Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2000:435658** HCAPLUS
DN **133:38600**
TI The use of subcutaneous **erythropoietin** and intravenous **iron** for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations
AU Silverberg, Donald S.; Wexler, Dov; Blum, Miriam; Keren, Gad; Sheps, David; Leibovitch, Eyal; Brosh, David; Laniado, Shlomo; Schwartz, Doron; Yachnin, Tatyana; Shapira, Itzhak; Gavish, Dov; Baruch, Ron; Koifman, Bella; Kaplan, Carl; Steinbruch, Shoshana; Iaina, Adrian
CS Department of Nephrology and Cardiology, Tel Aviv Medical Center, Tel Aviv-Jaffa, Israel
SO Journal of the American College of Cardiology (**2000**), 35(7), 1737-1744
CODEN: JACCDI; ISSN: 0735-1097
PB Elsevier Science Inc.
DT Journal
LA English
AB This study evaluated the prevalence and severity of anemia in patients with congestive heart failure (CHF) and the effect of its correction on cardiac and renal function and hospitalization. The prevalence and significance of mild anemia in patients with CHF is uncertain, and the role of **erythropoietin** with i.v. **iron** supplementation in treating this anemia is unknown. In a retrospective study, the records of the 142 patients in our CHF clinic were reviewed to find the prevalence and severity of anemia (Hb <12 g). In an intervention study, 26 of these patients, despite maximally tolerated therapy of CHF for at least six months, still had severe CHF and were also anemic. They were treated with s.c. **erythropoietin** and i.v. **iron** sufficient to increase the Hb to 12 g%. The doses of the CHF medications, except for diuretics, were not changed during the intervention period. The prevalence of anemia in the 142 patients increased with the severity of CHF, reaching 79.1% in those with New York Heart Association class IV. In the intervention study, the anemia of the 26 patients was treated for a mean of 7.2±5.5 mo. The mean Hb level and mean left ventricular ejection fraction increased significantly. The mean number of hospitalizations fell by 91.9% compared with a similar period before the study. The New York Heart Association class fell significantly, as did the doses of oral and i.v. furosemide. The rate of fall of the glomerular filtration rate slowed with the treatment. Anemia is very common in CHF and its successful treatment is associated with a significant improvement in cardiac function, functional class, renal function and in a marked fall in the need for diuretics and hospitalization.
IT **7439-89-6**, **Iron**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(use of s.c. **erythropoietin** and i.v. **iron** for treatment of anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations in humans)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

IT **11096-26-7**, **Erythropoietin**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of s.c. **erythropoietin** and i.v. **iron** for treatment of anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations in humans)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Albitar, S	1998	13	1206	Nephrol Dial Transpl	HCAPLUS
Anand, I	1993	70	357	Br Heart J	MEDLINE
Anand, I	1997	12	251	Curr Opin Cardiol	MEDLINE
Anon	1997	30	193	Am J Kidney Dis	
Anon	1994			Quick reference guid	
Anon	1992	20	32	US Renal Data System	
Besarab, A	1998	339	584	N Engl J Med	HCAPLUS
Carson, J	1995	170	32	Am J Surg	
Carson, J	1996	348	1055	Lancet	MEDLINE
Cline, C	1998	80	442	Heart	MEDLINE
Cowie, M	1997	18	208	Eur Heart J	HCAPLUS
Donnelly, S	1991	14	271	Clin Invest Med	MEDLINE
Elhalel-Dranitzki, M	1998	13	3041	Nephrol Dial Transpl	MEDLINE
Erturk, S	1999	14	1912	Nephrol Dial Transpl	HCAPLUS
Feelders, R	1998	28	520	Eur J Clin Invest	HCAPLUS
Fishbane, S	1995	26	41	Am J Kidney Dis	MEDLINE
Foley, R	1998	9	208	J Am Soc Nephrol	
Fonarow, G	1997	30	725	J Am Coll Cardiol	MEDLINE
Ghali, J	1988	148	2013	Arch Intern Med	MEDLINE
Goch, J	1996	73	403	Nephron	MEDLINE
Goicoechea, M	1998	54	1337	Kidney Intern	HCAPLUS
Goldberg, N	1992	124	424	Am Heart J	MEDLINE
Haber, H	1991	324	353	N Engl J Med	MEDLINE
Herrera-Garza, E	1999	115	1170	Chest	MEDLINE
Hochberg, Y	1974	4	224	J Multivar Anal	
Horl, W	1999	14	50	Nephrol Dial Transpl	
King, D	1996	25	144	Age Ageing	MEDLINE
Koch, K	1995	44	201	Clin Nephrol	HCAPLUS
Kooistra, M	1998	13	828	Nephrol Dial Transpl	
Kuriyama, S	1997	77	176	Nephron	HCAPLUS
Levine, B	1990	323	236	N Engl J Med	MEDLINE
Linde, T	1996	30	115	Scand J Urol Nephrol	MEDLINE
Locatelli, F	1998	13	1642	Nephrol Dial Transpl	MEDLINE
Lopez-Gomez, J	1995	10	31	Nephrol Dial Transpl	
Low, I	1989	31	26	Clin Nephrol	MEDLINE
Low-Friedrich, I	1991	11	54	Am J Nephrol	MEDLINE
Ma, J	1999	10	610	J Am Soc Nephrol	MEDLINE
Macdougall, I	1996	50	1694	Kidney Int	HCAPLUS
Macdougall, I	1998	13	3030	Nephrol Dial Transpl	MEDLINE
Maeda, K	1982	46	137	Jpn Circ J	MEDLINE
Maschio, G	1995	10	74	Nephrol Dial Transpl	
Massie, B	1996	11	221	Curr Opin Cardiol	MEDLINE
Michaelsen, A	1998	80	437	Heart	
Opasich, C	1996	78	354	Am J Cardiol	MEDLINE
Packer, M	1999	83	1	Am J Cardiol	

Reis, S	1997	30	733	J Am Coll Cardiol	MEDLINE
Rich, M	1996	44	638	J Am Geriatr Soc	MEDLINE
Rich, M	1995	333	1190	N Engl J Med	MEDLINE
Roth, D	1994	24	777	Am J Kidney Dis	MEDLINE
Scharer, K	1993	82	953	Acta Paediatr	MEDLINE
Schwengel, R	1994	73	908	Am J Cardiol	MEDLINE
Senni, M	1997	72	453	Mayo Clin Proc	MEDLINE
Silagy, C	1993	54	84	Clin Pharmacol Ther	MEDLINE
Silverberg, D	1996	27	234	Am J Kidney Dis	HCAPLUS
Silverberg, D	1999	55	79	Kidney Int	
Silverberg, D	1996	72	413	Nephron	HCAPLUS
Silverberg, D	1998	80	1	Nephron	MEDLINE
Volpe, M	1994	74	468	Am J Cardiol	MEDLINE
Wald, M	1995	71	190	Nephron	HCAPLUS
Weil, J	1995	310	827	Br Med J	MEDLINE
Yoshida, H	1998	53	880	Kidney Int	MEDLINE

L108 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:573162 HCAPLUS
DN 131:193985
TI The impact of withdrawing ACE inhibitors on **erythropoietin** responsiveness and left ventricular hypertrophy in hemodialysis patients
AU Erturk, Sehsuvar; Nergizoglu, Gokhan; Ates, Kenan; Duman, Neval; Erbay, Bulent; Karatan, Oktay; Ertug, A. Ergun
CS Department of Nephrology, Ankara University School of Medicine, Ibn-i Sina Hospital, Ankara, Turk.
SO Nephrology, Dialysis, Transplantation (**1999**), 14(8), 1912-1916
CODEN: NDTREA; ISSN: 0931-0509
PB Oxford University Press
DT Journal
LA English
AB Background. Angiotensin-converting enzyme (ACE) inhibitors have the capability of decreasing left ventricular mass index (LVMI) in chronic hemodialysis (HD) patients. On the other hand, recent reports provide conflicting information regarding the impact of ACE inhibitors on responsiveness to recombinant human **erythropoietin** (**rHuEpo**), and there are no data about the effect of withdrawing ACE inhibitors both on **rHuEpo** response and LVMI in HD patients. Methods. ACE inhibitors were switched to another antihypertensive medication in 23 out of 68 patients in our HD unit who were receiving both **rHuEpo** and an ACE inhibitor for more than 1 yr. Blood pressure at the pre- and post-dialysis phases, hematocrit levels and **rHuEpo** doses were determined at the end of the first and of the third years, and the LVMI was determined at the end of the third year. Statistical analyses were done in 15 patients in whom the study could be completed. Results. The mean (±SD) hematocrit level was increased from 26.3±6.4% to 29.8±6.3% at the first year ($P<0.05$), and to 29.4±6.5% at the third year ($P<0.05$ vs. before), while the mean dose of **rHuEpo** was decreased from 208.3±99.0 UI/kg/wk to 141.0±91.8 at the first year ($P=0.01$), and to 141.4±81.0 at the third year ($P=0.01$ vs. before). Administration of **rHuEpo** had been stopped in two patients at the end of the first year. The mean blood pressure level and the mean LVMI were not changed ($P>0.05$ vs. before). There were no significant changes in dialysis parameters, **iron** status, plasma renin activities, and levels of aldosterone, intact parathyroid hormone, aluminum and **erythropoietin.** Conclusion. The findings of this small uncontrolled study indicate that withdrawal of ACE inhibitors in hypertensive chronic HD patients receiving **rHuEpo** may result in an increase in hematocrit level, and a decrease in dose of **rHuEpo** without any significant changes in the blood pressure level and LVMI.

Controlled prospective studies are needed to clarify this issue.

IT **11096-26-7, Erythropoietin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(impact of withdrawing ACE inhibitors on **erythropoietin** responsiveness and left ventricular hypertrophy in humans on hemodialysis)

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Akpolat, T	1998	11	94	J Nephrol	MEDLINE
Albitar, S	1998	13	1206	Nephrol Dial Transpl	HCAPLUS
Bauer, J	1996		2331	The Kidney	
Cannella, G	1997	30	659	Am J Kidney Dis	HCAPLUS
Conlon, P	1994	9	1358	Nephrol Dial Transpl	MEDLINE
Constantinescu, C	1998	62	25	Immunol Lett	HCAPLUS
Cruz, D	1996	28	535	Am J Kidney Dis	HCAPLUS
Daugirdas, J	1993	4	1205	J Am Soc Nephrol	MEDLINE
Devereux, R	1986	57	450	Am J Cardiol	MEDLINE
Diez, J	1994	12	S31	J Hypertens	
Dyadyk, A	1997	12	945	Nephrol Dial Transpl	HCAPLUS
Erturk, S	1996	11	2050	Nephrol Dial Transpl	MEDLINE
Erturk, S	1996	11	396	Nephrol Dial Transpl	MEDLINE
Escbach, J	1988	11	203	Am J Kidney Dis	
Escbach, J	1997	30	S192	Am J Kidney Dis	
Goicoechea, M	1998	54	1337	Kidney Int	HCAPLUS
Gossmann, J	1996	50	973	Kidney Int	HCAPLUS
Gould, A	1990	181	225	Eur J Pharmacol	HCAPLUS
Gould, A	1980	96	523	J Lab Clin Med	HCAPLUS
Greaves, S	1994	24	768	Am J Kidney Dis	MEDLINE
Hirakata, H	1986	26	27	Clin Nephrol	MEDLINE
Julian, B	1998	9	1104	J Am Soc Nephrol	HCAPLUS
Kamper, A	1990	50	611	Scand J Clin Lab Inv	MEDLINE
Macdougall, I	1994	9	1032	Nephrol Dial Transpl	
Macdougall, I	1998	13	23	Nephrol Dial Transpl	
Morrone, L	1997	64	913	Transplantation	HCAPLUS
Motz, W	1987	10	S148	J Cardiovasc Pharmac	
Mrug, M	1997	100	2310	J Clin Invest	HCAPLUS
Naeshiro, I	1998	354	179	Eur J Pharmacol	HCAPLUS
Nakao, K	1967	29	754	Blood	HCAPLUS
Navarro, J	1998	80	239	Nephron	MEDLINE
Sahn, D	1978	58	1072	Circulation	MEDLINE
Sasaki, M	1996	12	1403	J Hypertens	
Schwenk, M	1998	18	627	Pharmacotherapy	HCAPLUS
Sennesael, J	1985	28	A252	Kidney Int	
Silberberg, J	1989	64	222	Am J Cardiol	MEDLINE
Silberberg, J	1990	6	1	Can J Cardiol	MEDLINE
Sundal, E	1991	6	955	Nephrol Dial Transpl	MEDLINE

L108 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1999:280686** HCAPLUS
DN **130:332154**
TI Is there a role for adjuvant therapy in patients being treated with **epoetin**?

AU Horl, W. H.
CS Department of Nephrology, University of Vienna, Vienna, Austria
SO Nephrology, Dialysis, Transplantation (**1999**), 14(Suppl. 2), 50-60
CODEN: NDTREA; ISSN: 0931-0509
PB Oxford University Press
DT Journal; General Review
LA English
AB A review with 78 refs. Adjuvant therapy may allow patients being treated with **epoetin** to derive greater clin. benefits. **Iron** supplementation is currently the most widely used form of adjuvant therapy; i.v. (i.v.) **iron** is required by the majority of haemodialysis patients receiving **epoetin.** Measurement of hypochromic red blood cells is the most direct way of assessing **iron** supply to the bone marrow. During the correction phase, a dose of i.v. **iron** equivalent to 50 mg/day is recommended, with the total dose not exceeding 3 g. When subclin. vitamin C deficiency is suspected, ascorbic acid may be given orally (1-1.5 g/wk) or i.v. (300 mg three times weekly at the end of dialysis). The active vitamin D metabolites alfacalcidol and calcitriol may, under some circumstances, improve anemia and reduce **epoetin** dosage requirements. Vitamin B6 requirements are increased during **epoetin** therapy, and supplementation at a dose of 100-150 mg/wk is recommended. Supplementation of vitamin B12 is optional. Folic acid is supplemented routinely in haemodialysis patients, though evidence that it increases the efficacy of **epoetin** is limited. Low doses (2-3 mg/wk) should normally be sufficient to maintain optimal folic acid stores in **epoetin**-treated patients, although higher doses are necessary for patients with hyperhomocysteinemia. L-Carnitine supplementation may be appropriate in some patients with anemia of chronic renal failure (CRF) unresponsive to, or requiring large doses of, **epoetin.** Androgens potentially could reduce **epoetin** costs in countries with limited resources, but should only be used in men older than 50 yr with a remnant kidney. Recent animal studies indicate that the combination of **epoetin** and insulin-like growth factor 1 might be beneficial in CRF patients. High doses of angiotensin-converting enzyme (ACE) inhibitors should be reserved for dialysis patients who have hypertension that cannot be controlled by other agents, or who require an ACE inhibitor for treatment of heart failure.
IT **7439-89-6**, **Iron**, biological studies **11096-26-7**, **Epoetin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**epoetin** and adjuvant therapy in humans)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Albitar, S	1994	9	1027	Nephrol Dial Transpl	
Albitar, S	1997	12	514	Nephrol Dial Transpl	HCAPLUS

Albitar, S	1997	12	514	Nephrol Dial Transpl	HCAPLUS
Albitar, S	1998	13	1206	Nephrol Dial Transpl	HCAPLUS
Argiles, A	1994	9	1809	Nephrol Dial Transpl	MEDLINE
Argiles, A	1994	9	1809	Nephrol Dial Transpl	MEDLINE
Azizi, M	1996	97	839	J Clin Invest	HCAPLUS
Ballal, S	1991	17	29	Am J Kidney Dis	MEDLINE
Barany, P	1997	29	565	Am J Kidney Dis	HCAPLUS
Barbour, G	1979	139	889	Arch Intern Med	MEDLINE
Berard, E	1992	62	368	Nephron	MEDLINE
Berns, J	1992	37	264	Clin Nephrol	MEDLINE
Boran, M	1996	73	314	Nephron	MEDLINE
Brox, A	1996	50	937	Kidney Int	HCAPLUS
Brox, A	1998	66	1053	Transplantation	HCAPLUS
Carozzi, S	1990	6	312	Adv Peritoneal Dial	MEDLINE
Carozzi, S	1997	43	M535	J Am Soc Artif Inter	MEDLINE
Christ, E	1997	82	2985	J Clin Endocrinol Me	HCAPLUS
Conlon, P	1994	9	1358	Nephrol Dial Transpl	MEDLINE
Consensus Group Stateme	1994	23	177	Dial Transplant	
Cruz, D	1996	28	535	Am J Kidney Dis	HCAPLUS
Descombes, E	1993	43	1319	Kidney Int	MEDLINE
Eder, M	1997	15	327	Stem Cells	HCAPLUS
Fishbane, S	1995	26	41	Am J Kidney Dis	MEDLINE
Gastaldello, K	1995	10	44	Nephrol Dial Transpl	
Gaughan, K	1997	30	495	Am J Kidney Dis	
Gobel, V	1994	153	43	Eur J Pediatr	MEDLINE
Goicoechea, M	1998	78	23	Nephron	HCAPLUS
Gokal, R	1979	48	393	Q J Med	MEDLINE
Golper, T	1992	5	94	Semin Dial	
Hampers, C	1967	276	551	N Engl J Med	MEDLINE
Hess, E	1996	11	749	Nephrol Dial Transpl	MEDLINE
Hunter, R	1970	1	61	Lancet	MEDLINE
Hutchison, F	1997	29	651	Am J Kidney Dis	
Julian, B	1994	46	1397	Kidney Int	MEDLINE
Kamper, A	1990	50	611	Scand J Clin Lab Inv	MEDLINE
Kasama, R	1996	27	680	Am J Kidney Dis	MEDLINE
Kooistra, M	1991	57	127	Nephron	MEDLINE
Kurtz, A	1990	122	323	Acta Endocrinol	HCAPLUS
Kurtz, A	1982	149	105	FEBS Lett	HCAPLUS
Kurtz, A	1988	85	7825	Proc Natl Acad Sci U	HCAPLUS
Labonia, W	1995	26	757	Am J Kidney Dis	HCAPLUS
Labonia, W	1987	32	754	Kidney Int	HCAPLUS
Lederle, R	1990	105	1307	Dtsch Med Wochenschr	
Macdougall, I	1989	299	157	Br Med J	MEDLINE
Macdougall, I	1992	304	225	Br Med J	MEDLINE
Macdougall, I	1996	50	1694	Kidney Int	HCAPLUS
Macdougall, I	1995	10	607	Nephrol Dial Transpl	MEDLINE
Matsumura, M	1996	72	574	Nephron	MEDLINE
Matsumura, M	1997	77	164	Nephron	HCAPLUS
Matsuzaki, Y	1996	63	33	Int J Hematol	MEDLINE
Moore, L	1992	3	105	J Renal Nutr	
Morrone, L	1997	64	913	Transplantation	HCAPLUS
Muta, K	1993	156	264	J Cell Physiol	HCAPLUS
Mydlik, M	1997	51	S56	Kidney Int	
Ono, K	1992	38	290	Clin Nephrol	MEDLINE
Pronai, W	1995	71	395	Nephron	HCAPLUS
Rao, D	1993	328	171	N Engl J Med	MEDLINE
Rolton, H	1991	6	440	Nephrol Dial Transpl	MEDLINE
Sanchez, J	1995	10	1476	Nephrol Dial Transpl	MEDLINE
Shimizu, T	1994	47	178	Am J Hematol	MEDLINE
Sunder-Plassmann, G	1995	10	2070	Nephrol Dial Transpl	MEDLINE

Taniguchi, S	1997	90	2244	Blood	HCAPLUS
Tarng, D	1998	9	227A	J Am Soc Nephrol	
Tarng, D	1998	13	2867	Nephrol Dial Transpl	HCAPLUS
Tarng, D	1997	3	S189	Nephrology	
Teruel, J	1996	7	140	J Am Soc Nephrol	HCAPLUS
Teruel, J	1996	30	129	Scand J Urol Nephrol	MEDLINE
Teruel, J	1996	30	403	Scand J Urol Nephrol	HCAPLUS
Tinawi, M	1996	74	291	Nephron	MEDLINE
Urena, P	1992	7	40	Nephrol Dial Transpl	MEDLINE
Urena, P	1991	59	384	Nephron	MEDLINE
Vihervuori, E	1996	87	2075	Blood	HCAPLUS
Vlahakos, D	1991	17	199	Am J Kidney Dis	MEDLINE
Vlahakos, D	1995	43	53	Clin Nephrol	MEDLINE
Walter, J	1993	8	1428	Nephrol Dial Transpl	MEDLINE
Westwood, N	1994	86	468	Br J Haematol	HCAPLUS
Zachee, P	1992	12	188	Am J Nephrol	MEDLINE

L108 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1998:588841** HCAPLUS
DN **130:762**
TI The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and **epoetin**
AU Besarab, Anatole; Bolton, Kline; Browne, Jeffrey K.; Egrie, Joan C.; Nissenson, Allen R.; Okamoto, Douglas M.; Schwab, Steve J.; Goodkin, David A.
CS Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, USA
SO New England Journal of Medicine (**1998**), 339(9), 584-590
CODEN: NEJMAG; ISSN: 0028-4793
PB Massachusetts Medical Society
DT Journal
LA English
AB In patients with end-stage renal disease, anemia develops as a result of **erythropoietin** deficiency, and recombinant human **erythropoietin** (**epoetin**) is prescribed to correct the anemia partially. We examined the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis. We studied 1233 patients with clin. evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients were assigned to receive increasing doses of **epoetin** to achieve and maintain a hematocrit of 42 percent, and 615 were assigned to receive doses of **epoetin** sufficient to maintain a hematocrit of 30 percent throughout the study. The median duration of treatment was 14 mo. The primary end point was the length of time to death or a first nonfatal myocardial infarction. After 29 mo, there were 183 deaths and 19 first nonfatal myocardial infarctions among the patients in the normal-hematocrit group and 150 deaths and 14 nonfatal myocardial infarctions among those in the low-hematocrit group (risk ratio for the normal-hematocrit group as compared with the low hematocrit group, 1.3; 95 percent confidence interval, 0.9 to 1.9). Although the difference in event-free survival between the two groups did not reach the prespecified statistical stopping boundary, the study was halted. The causes of death in the two groups were similar. The mortality rates decreased with increasing hematocrit values in both groups. The patients in the normal-hematocrit group had a decline in the adequacy of dialysis and received i.v. **iron** dextran more often than those in the low-hematocrit group. In patients with clin. evident congestive heart failure or ischemic heart disease who are receiving hemodialysis, administration of **epoetin** to raise their hematocrit to 42 percent is not recommended.
IT **11096-26-7**, **Epoetin**

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of normal as compared with low hematocrit values in humans with cardiac disease who are receiving hemodialysis and **epoetin**)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Barany, P	1996	7	1472	J Am Soc Nephrol abs	
Benz, R	1996	7	1473	J Am Soc Nephrol abs	
Beusterien, K	1996	7	763	J Am Soc Nephrol	HCAPLUS
Braumann, K	1991	58	129	Nephron	MEDLINE
Canadian Erythropoietin	1990	300	573	BMJ	
Cannella, G	1991	6	31	Nephrol Dial Transpl	MEDLINE
Collins, A	1994	5	439	J Am Soc Nephrol abs	
Collins, A	1997	8	190A	J Am Soc Nephrol abs	
Cox, D	1972	34	187	J R Stat Soc [B]	
Eschbach, J	1989	111	992	Ann Intern Med	MEDLINE
Eschbach, J	1993	4	425	J Am Soc Nephrol abs	
Eschbach, J	1993	6	180	Semin Dial	
Evans, R	1990	263	825	JAMA	MEDLINE
Goldberg, N	1992	124	424	Am Heart J	MEDLINE
Hoen, B	1995	10	377	Nephrol Dial Transpl	MEDLINE
Jennison, C	1990	5	299	Stat Sci	
Kusunoki, M	1981	1	413	J Cereb Blood Flow M	MEDLINE
Lan, K	1983	70	659	Biometrika	
Lowrie, E	1995			The anemia of ESRD a	
Lundin, A	1991	58	315	Nephron	MEDLINE
Macdougall, I	1990	335	614	Erratum Lancet	
Macdougall, I	1990	335	489	Lancet	MEDLINE
Marsh, J	1991	39	155	Kidney Int	MEDLINE
Massachusetts General H	1992	327	718	N Engl J Med	
McHorney, C	1993	31	247	Med Care	MEDLINE
Muirhead, N	1993	6	184	Semin Dial	
National Institute Of D	1996		23	Renal Data System US	
Nissenson, A	1996	7	1459	J Am Soc Nephrol abs	
Parfrey, P	1990	10	213	Am J Nephrol	MEDLINE
Parfrey, P	1991	2	2	J Am Soc Nephrol	MEDLINE
Pascual, J	1991	35	280	Clin Nephrol	MEDLINE
Rostand, S	1990		409	Clinical dialysis 2n	
Salonen, J	1992	86	803	Circulation	HCAPLUS
Sennesael, J	1991	40	121	Kidney Int	MEDLINE
Silberberg, J	1989	36	286	Kidney Int	MEDLINE
Sullivan, J	1981	1	1293	Lancet	HCAPLUS
Tielemans, C	1989	4	883	Nephrol Dial Transpl	MEDLINE
Veys, N	1992	19	358	Am J Kidney Dis	MEDLINE
Wizemann, V	1992	62	161	Nephron	MEDLINE
Zehnder, C	1992	61	21	Nephron	MEDLINE

L108 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1998:329025** HCAPLUS
DN **129:67164**
TI The estimation of efficacy of oral **iron** supplementation during treatment with **epoetin beta** (recombinant human

erythropoietin) in patients undergoing cardiac surgery
AU Sowade, Olaf; Messinger, Diethelm; Franke, Werner; Sowade, Birgit; Scigalla, Paul; Warnke, Harry
CS Department of Cardiac Surgery, Charite-Hospital, Humboldt University Berlin, Mannheim, Germany
SO European Journal of Haematology (**1998**), 60(4), 252-259
CODEN: EJHAEC; ISSN: 0902-4441
PB Munksgaard International Publishers Ltd.
DT Journal
LA English
AB We estimated the efficacy of oral **iron** therapy during treatment with rhEPO (**erythropoietin**) in patients undergoing cardiac surgery who were contraindicated for autologous blood donation. Seventy-six patients were enrolled in this double-blind, placebo-controlled trial and assigned to the 2 treatment groups (5+500 U/kg body weight rhEPO or placebo i.v. over 14 d before surgery). During the treatment period all patients received 300 mg Fe2+ (**iron** glycine sulfate) orally per day. RhEPO therapy produced significant increases in Hb concentration (Hb), reticulocyte count, hematocrit (Hct) and the hypochromic red blood cells (HRBC), and a decrease in transferrin saturation (41%) compared to the placebo group before surgery. However, the preoperative increase in HRBC was independent of the baseline ferritin and even correlated pos. with the preoperative increase in Hct ($r=0.47$, $p<0.01$). In rhEPO patients there were inverse correlations between baseline serum **iron** and the preoperative increases in Hb ($r=-0.39$, $p<0.05$), Hct ($r=-0.50$, $p<0.01$) and HRBC ($r=-0.53$, $p<0.001$). With this treatment regimen the HRBC appear to reflect the degree of erythropoietic stimulation rather than functional **iron** deficiency. The preoperative increases in reticulocytes, HRBC and Hb/Hct in patients with ferritin <100 mg/l or transferrin saturation <16% showed no significant difference compared to their complementary groups. The preoperative decrease in storage **iron** and the inverse correlation between the baseline ferritin and the preoperative change in ferritin ($r=-0.94$, $p<0.0001$) in the rhEPO group indicate that the **iron** requirement for Hb synthesis is probably covered by the breakdown of stored **iron** and an increase in the rate of absorption of orally administered Fe2+. I.v. rhEPO treatment with 5+500 U/kg body weight in combination with 300 mg oral Fe2+/d given over 14 d before surgery is a suitable regimen to increase Hb by about 1.61 g/dL and Hct by 0.06.
IT **7439-89-6**, **Iron**, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(deficiency; estimation of efficacy of oral **iron** supplementation during treatment with **epoetin beta** (recombinant human **erythropoietin**) in patients undergoing cardiac surgery)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

IT **7439-89-6D**, **Iron**, glycine sulfate complexes, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(estimation of efficacy of oral **iron** supplementation during treatment with **epoetin beta** (recombinant human **erythropoietin**) in patients undergoing cardiac surgery)
RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

IT **11096-26-7, Erythropoietin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rhEPO; estimation of efficacy of oral **iron** supplementation during treatment with **epoetin beta** (recombinant human **erythropoietin**) in patients undergoing cardiac surgery)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adamson, J	1993		161	Erythropoietin - mol	HCAPLUS
Beguin, Y	1997	90	A36	Blood	
Biesma, D	1994	86	30	Br J Haematol	MEDLINE
Brugnara, C	1993	81	956	Blood	MEDLINE
Brugnara, C	1994	123	660	J Lab Clin Med	HCAPLUS
Brunner, W	1995	5	122	J Suisse Pharm	
Canadian Orthopedic Per	1993	341	1227	Lancet	
Cavill, I	1975	256	328	Nature	HCAPLUS
Cazzola, M	1997	89	4248	Blood	HCAPLUS
Cook, J	1990	51	301	Am J Clin Nutr	HCAPLUS
Cook, J	1986	68	726	Blood	MEDLINE
Cook, J	1990	75	603	Br J Haematol	MEDLINE
Donohue, D	1958	37	1564	J Clin Invest	MEDLINE
Eschbach, J	1991	88	72	Contrib Nephrol	MEDLINE
Eschbach, J	1987	316	73	N Engl J Med	MEDLINE
Finch, C	1982	60	1241	Blood	HCAPLUS
Goodnough, L	1991	188	289	J Lab Clin Med	
Goodnough, L	1989	321	1163	N Engl J Med	MEDLINE
Horl, W	1996	11	246	Nephrol Dial Transpl	MEDLINE
Kumpf, V	1990	24	162	Ann Pharmacother	MEDLINE
Macdougall, I	1992	304	225	Br Med J	MEDLINE
Mercuriali, F	1995	6	67	Erythropoiesis	
Mercuriali, F	1993	33	55	Transfusion	MEDLINE
Meyer, M	1996	129	258	J Pediatr	HCAPLUS
Nadler, S	1962	51	224	Surgery	
Price, T	1996	36	29	Transfusion	MEDLINE
Silverberg, D	1996	72	413	Nephron	HCAPLUS
Skikne, B	1990	75	1870	Blood	HCAPLUS
Skikne, B	1993		177	Erythropoietin - mol	HCAPLUS
Skikne, B	1992	120	746	J Lab Clin Med	HCAPLUS
Sowade, O	1997	55	89	Am J Hematol	HCAPLUS
Sowade, O	1997	89	411	Blood	HCAPLUS
Sowade, O	1997	129	97	J Lab Clin Med	HCAPLUS

L108 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1998:88081** HCAPLUS
DN **128:124107**
TI Evaluation of erythropoietic activity on the basis of the red cell and reticulocyte distribution widths during **epoetin beta** therapy in patients undergoing cardiac surgery

AU Sowade, Olaf; Sowade, Birgit; Gross, Johann; Brilla, Kay; Ziemer, Sabine; Franke, Werner; Stephan, Peter; Scigalla, Paul; Warnke, Harry
CS Dep. Heart Surgery, Medical Fac., Humboldt Univ., Berlin, Germany
SO Acta Haematologica (**1998**), 99(1), 1-7
CODEN: ACHAAH; ISSN: 0001-5792
PB S. Karger AG
DT Journal
LA English
AB The changes in the red cell and reticulocyte distribution widths during preoperative treatment with recombinant human **erythropoietin** (rhEPO) were evaluated in a double-blind, placebo-controlled trial in cardiac surgery patients. The increases in the reticulocyte count, in the Hb and in all distribution widths are the expression of the marked preoperative stimulation of erythropoiesis in the patients treated with rhEPO. Only placebo patients with a Hb ≤ 7.5 mmol/l or a transferrin > 4.0 g/l at baseline showed an increase in the red cell distribution width or in the reticulocyte Hb distribution width on oral **iron** therapy alone. While the reticulocyte count and the distribution widths of red cells in the rhEPO patients decreased postoperatively, only the increases in the distribution widths of reticulocytes after the second postoperative day indicate that stimulation of erythropoiesis had taken place. In patients with a low Hb or a high transferrin the rhEPO therapy should be preceded by **iron** therapy in order to raise the Hb level and reduce the cost of treatment.
IT **122312-54-3**, **Epoetin beta**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of erythropoietic activity on the basis of the red cell and reticulocyte distribution widths during **epoetin beta** therapy in patients undergoing cardiac surgery)
RN 122312-54-3 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1997:466755** HCAPLUS
DN **127:131546**
TI Kinetics of reticulocyte maturity fractions and indices and **iron** status during therapy with **epoetin beta** (recombinant human **erythropoietin**) in cardiac surgery patients
AU Sowade, Olaf; Sowade, Birgit; Brilla, Kay; Franke, Werner; Stephan, Peter; Gross, Johann; Scigalla, Paul; Warnke, Harry
CS Cardiac Surgery Clinic, Medical Faculty (Charite), Humboldt University, Berlin, Germany
SO American Journal of Hematology (**1997**), 55(2), 89-96
CODEN: AJHEDD; ISSN: 0361-8609
PB Wiley-Liss
DT Journal
LA English
AB We evaluated the changes in reticulocyte maturity fractions and indexes, as measured by flow cytometry, during preoperative treatment with recombinant human **erythropoietin** (**epoetin beta**) in cardiac surgery patients. A total of 72 patients was enrolled in this double-blind, randomized, placebo-controlled clin. trial and assigned to the two treatment groups (5 + 500 U/kg bodyweight **epoetin beta** or placebo i.v. over 14 days preoperatively). Therapy with **epoetin beta** produced continuous increases in

hematocrit/Hb, in the most mature fraction of reticulocytes (LR), and in reticulocyte count. In the first treatment week there were parallel increases in the fraction of most immature reticulocytes (HR) and in the reticulocyte mean cell volume During the second week of treatment the reticulocyte mean cell Hb content (CHr) decreased, but CHr was independent of all **iron** parameters, affecting neither the reticulocyte fractions nor the hematocrit/Hb increase. The total preoperative rise in hematocrit correlated with the rises in LR fraction (P = 0.0270) and reticulocyte count (P = 0.0486) during the first week of treatment. Whereas in the **epoetin beta** patients the preoperative change in HR fraction showed neg. correlations with transferrin saturation at baseline (P = 0.0058) and with the preoperative change in **iron** (P = 0.0113), the preoperative change in the LR fraction correlated pos. with transferrin at baseline (P = 0.0115). Postoperatively, the reticulocyte parameters revealed that the onset of increased stimulation of erythropoiesis did not occur in the placebo patients until the second postoperative day, whereas erythropoietic activity in the **epoetin beta** patients was much higher during the postoperative period as well, as a result of the preoperative stimulation of erythropoiesis. The reticulocyte parameters measured by flow cytometry permitted an objective anal. of erythropoietic activity during treatment with **epoetin beta** and in all patients post-operatively. Further studies in various types of **epoetin beta** therapy are needed in order to clarify the value of these reticulocyte parameters for identification of **iron** deficiency and optimization of **epoetin beta** treatment regimen.

IT **7439-89-6**, **Iron**, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(kinetics of reticulocyte maturity fractions and indexes and **iron** status during therapy with **epoetin beta** in cardiac surgery patients)

RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

IT **122312-54-3**, **Epoetin beta**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(kinetics of reticulocyte maturity fractions and indexes and **iron** status during therapy with **epoetin beta** in cardiac surgery patients)

RN 122312-54-3 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adamson, J	1968	44	725	Am J Med	MEDLINE
Bidstrup, B	1993	55	971	Ann Thorac Surg	MEDLINE
Brugnara, C	1994	102	623	Am J Clin Pathol	MEDLINE
Brugnara, C	1994	123	660	J Lab Clin Med	HCAPLUS
Eschbach, J	1987	316	73	N Engl J Med	MEDLINE

Ganzoni, A	1969	16	119	Br J Haematol	MEDLINE
Goodnough, L	1989	321	1163	N Engl J Med	MEDLINE
Kampf, D	1989	76	106	Contrib Nephrol	MEDLINE
Labardini, J	1973	7	301	Haematology	HCAPLUS
Lee, L	1986	7	508	Cytometry	HCAPLUS
Levine, E	1989	106	432	Surgery	MEDLINE
Lowenstein, L	1959	8	135	Int Rev Cytol	HCAPLUS
Rapoport, S	1986		1	The Reticulocyte	
Schmoeckel, M	1993	41	364	Thorac Cardiovasc Su	MEDLINE
Sowade, O	1995	44	257	Anaesthesist	MEDLINE
Sowade, O	1997	89	411	Blood	HCAPLUS
Sowade, O	1995	33	37a	Eur J Clin Chem Clin	
Tatsumi, N	1990	82	41	Contrib Nephrol	MEDLINE
Wells, D	1992	97	130	Am J Clin Pathol	MEDLINE
Yataganas, X	1970	62	254	Exp Cell Res	MEDLINE

L108 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1997:51720** HCAPLUS
DN **126:127308**
TI Avoidance of allogeneic blood transfusions by treatment with **epoetin beta** (recombinant human **erythropoietin**) in patients undergoing open-heart surgery
AU Sowade, Olaf; Warnke, Harry; Scigalla, Paul; Sowade, Birgit; Franke, Werner; Messinger, Diethelm; Gross, Johann
CS Med. Fac., Humboldt Univ., Berlin, Germany
SO Blood (**1997**), 89(2), 411-418
CODEN: BLOOAW; ISSN: 0006-4971
PB Saunders
DT Journal
LA English
AB In a double-blind, randomized, placebo-controlled trial, we evaluated the ability of **epoetin beta** (recombinant human **erythropoietin**) to avoid allogeneic blood transfusions (ABT) and the associated risks in patients undergoing primary elective open-heart surgery and in whom autologous blood donation (ABD) was contraindicated. Seventy-six patients overall were enrolled onto the trial and were randomly assigned to the two treatment groups, 5+500 U/kg body weight (BW) **epoetin beta** or placebo i.v. over 14 days preoperatively. All patients received 300 mg Fe2+ orally per day during the treatment period. Preoperatively, the mean Hb increase was 1.50 g/dL greater in **epoetin beta** patients than in placebo patients (95% confidence interval, 1.10 to 1.90 g/dL), allowing a rapid return to the baseline value by the seventh postoperative day in most **epoetin beta** patients. The mean volume of blood collected by intraoperative isovolemic hemodiln. was 562 mL (red blood cell mass, 274 mL) in the **epoetin beta** group and 218 mL (red blood cell mass, 94 mL) in the placebo group, resp. Only four patients (11%) in the **epoetin beta** group received an ABT, compared with 19 (53%) in the placebo group. **Epoetin beta** was most useful in patients with a perioperative blood loss greater than 750 mL, in those with a baseline hematocrit value less than 0.42, and in those aged ≥60 yr. The **iron** supplementation proved adequate despite the fact that a significant decrease in ferritin (median, 48.1%) and transferrin saturation (median, 40.5%) was observed in **epoetin beta** patients preoperatively. No influence of **epoetin beta** therapy on blood pressure, laboratory safety variables, or the frequency of specific adverse events was observed I.v. **epoetin beta** treatment of 5+500 U/kg BW in combination with 300 mg Fe2+ orally per day administered over 14 days preoperatively is an adequate therapy for increasing mean Hb levels by

approx. 1.50 g/dL and reducing the allogeneic blood requirement in patients undergoing elective open-heart surgery and in whom ABD is contraindicated.

IT **7439-89-6**, **Iron**, biological studies **122312-54-3**
, **Epoetin beta**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(avoidance of allogeneic blood transfusions by treatment with **epoetin beta** (recombinant human **erythropoietin**) in combination with **iron** in patients undergoing open-heart surgery)

RN 7439-89-6 HCAPLUS
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)

Fe

RN 122312-54-3 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bidstrup, B	1993	55	971	Ann Thorac Surg	MEDLINE
Biesma, D	1994	344	367	Lancet	MEDLINE
Bommer, J	1988	2	406	Lancet	MEDLINE
Brugnara, C	1994	123	660	J Lab Clin Med	HCAPLUS
Canadian Orthopedic Per	1993	341	1227	Lancet	
Casagrande, J	1978	34	483	Biometrics	MEDLINE
Cosgrove, D	1985	40	380	Ann Thorac Surg	MEDLINE
Duke, M	1969	39	503	Circulation	MEDLINE
Eschbach, J	1987	316	73	N Engl J Med	MEDLINE
Geraci, J	1993	118	18	Ann Intern Med	MEDLINE
Goodnough, L	1995	60	473	Ann Thorac Surg	MEDLINE
Goodnough, L	1991	266	86	JAMA	
Goodnough, L	1989	321	1163	N Engl J Med	MEDLINE
Hammermeister, K	1990	82	IV-380	Circulation	
Hollander, M	1973			Nonparametric Statis	
Knight, A	1988	68	681	Anesthesiology	MEDLINE
Kyo, S	1992	86	II-413	Circulation	
Kyo, S	1992	86	II-17	Circulation abstr 28	
Levine, E	1989	106	432	Surgery	MEDLINE
Lewis, C	1991	51	448	Ann Thorac Surg	MEDLINE
McDougall, I	1989	299	157	Br Med J	
McMahon, F	1990	76	1718	Blood	HCAPLUS
Nadler, S	1962	51	224	Surgery	
Price, T	1996	36	29	Transfusion	MEDLINE
Robertie, P	1990	28	197	Int Anaesthesiol Cli	MEDLINE
Rutherford, C	1994	96	139	Am J Med	MEDLINE
Schmoeckel, M	1993	41	364	Thorac Cardiovasc Su	MEDLINE
Schooley, J	1987	67	11	Br J Haematol	HCAPLUS
Scott, W	1992	103	1001	J Thorac Cardiovasc	MEDLINE
Skikne, B	1992	120	746	J Lab Clin Med	HCAPLUS
Sowade, O	1995	44	257	Anaesthesist	MEDLINE
Sowade, O	1995	86	352a	Blood	

Welch, H |1992 |116 |393 |Ann Intern Med |MEDLINE

L108 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1996:309221** HCAPLUS
DN **125:2127**
TI Perioperative **epoetin alfa** reduces transfusion requirements in coronary artery bypass graft surgery
AU D'Ambra, Michael
CS Massachusetts General Hospital, Boston, MA, 02114, USA
SO Seminars in Hematology (**1996**), 33(2, Suppl. 2), 73-74
CODEN: SEHEA3; ISSN: 0037-1963
PB Saunders
DT Journal
LA English
AB Patients undergoing cardiac surgery continue to be exposed to allogeneic blood. **Epoetin alfa** has been shown to reduce allogeneic blood requirements in patients scheduled for cardiac surgery, principally by facilitating autologous blood (AB) predonation. However, for some patients, there may not be sufficient time to donate AB prior to surgery. In this group of patients, the perisurgical use of **epoetin alfa** (recombinant human **erythropoietin** ; **EPREX** Janssen-Cilag, New Brunswick, NJ) warrants further investigation as a means of reducing allogeneic blood exposure. The results of an early double-blind study in 41 CABG patients suggested that perisurgical administration of **epoetin alfa** reduces postoperative allogeneic transfusion requirements without causing a significant increase in preoperative hematocrit (Hct). In a double-blind, placebo-controlled, parallel-group study in 182 patients scheduled for coronary artery bypass graft (CABG) surgery, **epoetin alfa** was administered perisurgically by s.c. (SC) injection (150 or 300 IU/kg/d for 5 days prior to surgery, on the day of surgery, and for 2 days postoperatively). All patients received oral **iron** supplementation for 5 days preoperatively. The intent-to-treat anal. showed that **epoetin alfa** reduced the percentage of patients exposed to allogeneic blood postoperatively compared with placebo, but not significantly. However, when the patients who developed surgical complications were excluded from the anal., the effect of **epoetin alfa** became significant (Fig 1). Reticulocytosis following surgery was significantly increased in patients treated with **epoetin alfa** 300 IU/kg. Although hematocrit (Hct) levels were significantly higher in **epoetin alfa**-treated patients during the first 7 days postoperatively, Hct levels prior to surgery were comparable among **epoetin alfa**- and placebo-treated patients. **Epoetin alfa** was well tolerated, and the overall postoperative mortality rate for patients treated with **epoetin alfa** was similar to that reported in other studies. Perisurgical administration of **epoetin alfa** therefore decreases exposure to allogeneic blood in patients undergoing CABG surgery who do not experience surgical complications. However, the optimum dosage regimen remains to be defined.
IT **113427-24-0**, **Epoetin alfa**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(perioperative **epoetin alfa** reduces transfusion requirements in humans having coronary artery bypass graft surgery)
RN 113427-24-0 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1996:309220** HCAPLUS
DN **125:2126**
TI Subcutaneous **epoetin alfa** as an adjunct to autologous blood donation before elective coronary artery bypass graft surgery
AU Gombotz, Hans
CS Department Anesthesiology, University Graz, Graz, A-8036, Austria
SO Seminars in Hematology (**1996**), 33(2, Suppl. 2), 69-72
CODEN: SEHEA3; ISSN: 0037-1963
PB Saunders
DT Journal
LA English
AB Autologous blood (AB) donation can minimize exposure to allogeneic blood in patients scheduled for coronary artery bypass graft (CABG) surgery. During AB donation in this group of patients, minimization of the accompanying decrease in Hb levels is important to reduce the risk of provoking silent myocardial ischemia and/or arrhythmias. Recombinant human **erythropoietin** (**rHuEPO**) has been used to facilitate AB donation and minimize the accompanying decrease in Hb levels in patients scheduled for cardiac surgery. In 24 patients scheduled for CABG surgery, once-weekly s.c. (SC) administration of **rHuEPO** (**epoetin alfa** 400 IU/kg) plus oral **iron** supplementation for 4 wk prior to surgery caused marked stimulation of erythropoiesis and significantly increased collection of autologous red blood cells (RBCs) compared with oral **iron** alone. Furthermore, **epoetin alfa** minimized the decrease in Hb levels associated with AB donation and significantly attenuated allogeneic blood requirements by facilitating the collection of 4 AB units prior to surgery. During AB donation, no changes in the incidence or severity of ischemic attacks or ST-segment changes were observed using electrocardiog. monitoring. **Epoetin alfa** was well tolerated. Once-weekly SC administration of **epoetin alfa** for 4 wk therefore represents a practical means of facilitating AB donation by patients scheduled for CABG surgery.
IT **113427-24-0**, **Epoetin alfa**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(s.c. **epoetin alfa** as an adjunct to autologous blood donation before elective coronary artery bypass graft surgery in humans)
RN 113427-24-0 HCAPLUS
CN 1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L108 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1996:309219** HCAPLUS
DN **125:1483**
TI Autologous blood donation with recombinant human **erythropoietin** in cardiac surgery: The Japanese experience
AU Baron, Jean-Francois
CS Service d'Anesthesie Reanimation Chirurgicale, Hopital R. Broussais, Paris, 75674/14, Fr.
SO Seminars in Hematology (**1996**), 33(2, Suppl. 2), 64-68
CODEN: SEHEA3; ISSN: 0037-1963
PB Saunders

DT Journal; General Review
LA English
AB A review with 9 refs. Four units of predonated autologous blood (AB) is considered sufficient to cover the blood requirements of 95% of patients undergoing elective cardiac surgery, thus avoiding the risks associated with allogeneic blood transfusion. A review of six Japanese studies was undertaken to summarize the potential for recombinant human **erythropoietin** (**rHuEPO**) to facilitate donation of AB by patients scheduled for cardiac surgery. I.v. (IV) administration of **rHuEPO** improved the anemia associated with AB donation, an effect that was further enhanced by IV **iron** supplementation. Once weekly s.c. (SC) administration of **rHuEPO** facilitated the donation of AB and reduced allogeneic blood requirements in patients scheduled for cardiac surgery, suggesting that **rHuEPO** could be administered on an outpatient basis. **rHuEPO** was of particular benefit in anemic patients, eliminating exposure to allogeneic blood in the majority of patients. In conclusion, **rHuEPO** facilitates the donation of AB and reduces allogeneic blood requirements of patients scheduled for cardiac surgery.
IT **11096-26-7**, **Erythropoietin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(autologous blood donation with recombinant human **erythropoietin** in Japanese cardiac surgery)
RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> fil reg
FILE 'REGISTRY' ENTERED AT 15:25:36 ON 23 AUG 2005
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STRUCTURE FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2
DICTIONARY FILE UPDATES: 22 AUG 2005 HIGHEST RN 861291-85-2

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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
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Structure search iteration limits have been increased. See HELP SLIMITS

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http://www.cas.org/ONLINE/DBSS/registryss.html

=> => d ide can l112

L112 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN **25322-68-3** REGISTRY
ED Entered STN: 16 Nov 1984
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN α,ω-Hydroxypoly(ethylene oxide)
CN α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)
CN α-Hydro-ω-hydroxypoly(oxyethylene)
CN 1,2-Ethanediol, homopolymer
CN 1660O
CN 1660S
CN 400DAB8
CN Alkox
CN Alkox E 100
CN Alkox E 130
CN Alkox E 160
CN Alkox E 240
CN Alkox E 30
CN Alkox E 30G
CN Alkox E 45
CN Alkox E 60
CN Alkox E 75
CN Alkox R 100
CN Alkox R 1000
CN Alkox R 15
CN Alkox R 150
CN Alkox R 400
CN Alkox SR
CN Alkox SW
CN Antarox E 4000
CN Aquacide III
CN Aquaffin
CN Badimol
CN BDH 301
CN Bradsyn PEG
CN Breox 2000
CN Breox 20M
CN Breox 4000
CN Breox 550
CN Breox PEG 300
CN CAFO 154
CN Carbowax
CN Carbowax 100
CN Carbowax 1000
CN Carbowax 1350
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CN Carbowax 20

CN Carbowax 200
CN Carbowax 20000
CN Carbowax 25000
CN Carbowax 300
CN Carbowax 3350
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MF (C2 H4 O)n H2 O
CI PMS, COM
PCT Polyether
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SCISEARCH, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
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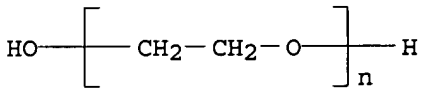

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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22615 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
84192 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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REFERENCE 2: 143:165571

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REFERENCE 9: 143:162006

REFERENCE 10: 143:161849

=> d ide can l111 tot

L111 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN **20074-52-6** REGISTRY
ED Entered STN: 16 Nov 1984
CN Iron, ion (Fe3+) (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Fe3+
CN Ferric cation
CN Ferric ion
CN Iron (Fe3+)
CN Iron ion(3+)
CN Iron trivalent ion
CN Iron(3+)
CN Iron(3+) ion
CN Iron(III) cation
CN Iron(III) ion
MF **Fe**
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, NIOSHTIC, PIRA, PROMT, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)

Fe^{3+}

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10606 REFERENCES IN FILE CA (1907 TO DATE)
690 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
10624 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 143:163763

REFERENCE 2: 143:160506

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REFERENCE 5: 143:158665

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REFERENCE 7: 143:157906

REFERENCE 8: 143:157868

REFERENCE 9: 143:157295

REFERENCE 10: 143:156829

L111 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN **15438-31-0** REGISTRY
ED Entered STN: 16 Nov 1984
CN Iron, ion (Fe2+) (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Fe2+
CN Ferrous cation
CN Ferrous ion
CN Iron (Fe2+)
CN Iron dication
CN Iron divalent ion
CN Iron ion(2+)
CN Iron(2+)
CN Iron(II) ion
MF **Fe**
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSNB, DETHERM*, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL
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Fe^{2+}

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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REFERENCE 10: 143:157906

L111 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN **7439-89-6** REGISTRY
ED Entered STN: 16 Nov 1984
CN **Iron (7CI, 8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:

CN 300A
CN 3ZhP
CN A 131
CN A 227
CN AC 325
CN Ancor B
CN Ancor EN 80/150
CN Ancor Image 100
CN AQ 80
CN Armco 80
CN Armco iron
CN ASC 300
CN ASC 300 (metal)
CN Atomel 300M200
CN Atomel 500M
CN Atomet 28
CN Atomet 95
CN Atomet 95G
CN Atomet 95SP
CN Atomiron 44MR
CN Atomiron 5M
CN Atomiron AFP 25
CN Atomiron AFP 5
CN ATW 230
CN ATW 432
CN BASF-EW
CN Carbon 0.17, iron 99.83 (atomic)
CN Carbonyl iron
CN CM
CN CM (iron)
CN Copy Powder CS 105-175
CN DH
CN DKP
CN DKP (metal)
CN DM 96
CN DM 96 (iron)
CN DNK 2R
CN DSP 1000
CN DSP 128B
CN DSP 135
CN DSP 135C
CN DSP 138
CN EF 1000
CN EF 250
CN EFV
CN EFV 200/300
CN EFV 250
CN EFV 250/400
CN Electrolytic iron
CN EO 5A
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DR 8011-79-8, 8053-60-9, 129048-51-7, 73135-38-3, 70884-35-4, 39344-71-3, 190454-13-8, 195161-83-2, 199281-22-6, 443783-52-6, 675141-17-0
MF **Fe**
CI COM
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ENCOMPPAT2, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*,
MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, ULIDAT,
USPAT2, USPATFULL, VETU, VTB
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Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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21949 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
414665 REFERENCES IN FILE CAPLUS (1907 TO DATE)
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REFERENCE 8: 143:165522

REFERENCE 9: 143:165278

REFERENCE 10: 143:165232

=> d ide can l110 tot

L110 ANSWER 1 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **702719-62-8** REGISTRY
ED Entered STN: 02 Jul 2004
CN **Erythropoietin (human) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 2: PN: WO2004047858 SEQID: 2 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:34188

L110 ANSWER 2 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **702719-61-7** REGISTRY
ED Entered STN: 02 Jul 2004
CN **Erythropoietin (human) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 1: PN: WO2004047858 SEQID: 1 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:34188

L110 ANSWER 3 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **681860-67-3** REGISTRY
ED Entered STN: 14 May 2004
CN **Erythropoietin (human 165-amino acid isoform) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 73: PN: WO2004033651 SEQID: 73 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:352406

L110 ANSWER 4 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **668496-69-3** REGISTRY
ED Entered STN: 29 Mar 2004
CN **Erythropoietin (human 166-amino acids variant) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 2: PN: WO2004019972 SEQID: 2 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:229921

L110 ANSWER 5 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **668496-68-2** REGISTRY
ED Entered STN: 29 Mar 2004
CN **Erythropoietin (human 165-amino acids variant) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 1: PN: WO2004019972 SEQID: 1 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:229921

L110 ANSWER 6 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **510776-48-4** REGISTRY
ED Entered STN: 06 May 2003
CN **29-165-erythropoietin (human) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: WO03029291 SEQID: 1 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:298131

L110 ANSWER 7 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **510776-47-3** REGISTRY
ED Entered STN: 06 May 2003
CN **Erythropoietin (human 166-amino acid isoform) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 2: PN: WO03029291 SEQID: 2 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN

SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:298131

L110 ANSWER 8 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **510776-46-2** REGISTRY
ED Entered STN: 06 May 2003
CN **Erythropoietin (human 165-amino acid isoform) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 1: PN: WO03029291 SEQID: 1 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 138:298131

L110 ANSWER 9 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **221039-34-5** REGISTRY
ED Entered STN: 08 Apr 1999
CN **Erythropoietin (human) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 1: PN: WO0027869 SEQID: 1 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
5 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:91083

REFERENCE 2: 132:352760

REFERENCE 3: 132:31780

REFERENCE 4: 130:357233

REFERENCE 5: 130:218746

L110 ANSWER 10 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209810-58-2** REGISTRY
ED Entered STN: 12 Aug 1998
CN **Erythropoietin [30-asparagine,32-threonine,87-valine,88-asparagine,90-threonine] (human) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Aranesp
CN Bone morphogenic protein 7
CN Darbepoetin alfa
CN Darbepoetin alpha
CN **erythropoietin [30-asparagine,32-threonine,87-valine,88-asparagine,90-threonine] (human)**
CN KRN 321
CN NESP
CN Nespo
CN Ostogenes protein 1
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CAS Client Services
LC STN Files: ADISINSIGHT, BIOSIS, CA, CANCERLIT, CAPLUS, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PROUSDDR, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

134 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
134 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 143:133095

REFERENCE 2: 143:110178

REFERENCE 3: 143:89919

REFERENCE 4: 143:72269

REFERENCE 5: 143:72173

REFERENCE 6: 143:72169

REFERENCE 7: 143:71862

REFERENCE 8: 143:71764

REFERENCE 9: 143:19957

REFERENCE 10: 143:19576

L110 ANSWER 11 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **134547-95-8** REGISTRY
ED Entered STN: 28 Jun 1991
CN **1-165-Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 1: PN: EP1064951 SEQID: 1 claimed protein
CN 1: PN: WO0102017 SEQID: 1 claimed protein
CN 1: PN: WO0187329 SEQID: 1 claimed protein
CN 2: PN: WO0130320 SEQID: 1 unclaimed protein
CN 4: PN: WO0032772 TABLE: 1 claimed protein
CN **Erythropoietin (human 165-amino acid variant)**
CN **Erythropoietin (human isoform 1)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, IMSPATENTS, IMSRESEARCH, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
7 REFERENCES IN FILE CA (1907 TO DATE)
7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:11065

REFERENCE 2: 134:331598

REFERENCE 3: 134:105827

REFERENCE 4: 134:91083

REFERENCE 5: 133:38711

REFERENCE 6: 115:199743

REFERENCE 7: 115:23689

L110 ANSWER 12 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **122312-54-3** REGISTRY
ED Entered STN: 25 Aug 1989
CN **1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform β (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN BM 06.019
CN EPOCH
CN Epoetin beta
CN Epogin
CN Marogen
CN NeoRecormon
CN NeoRecormon Multidose Vials
CN Recormon
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR US Adopted Names Council (USAN)
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CIN, CSNB, DDFU,

DIOGENES, DRUGU, EMBASE, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS,
IMSRESEARCH, IPA, MEDLINE, MRCK*, PIRA, PROMT, PROUSDDR, RTECS*,
SCISEARCH, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

101 REFERENCES IN FILE CA (1907 TO DATE)
101 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 143:120713

REFERENCE 2: 143:72269

REFERENCE 3: 143:1642

REFERENCE 4: 142:476541

REFERENCE 5: 142:404682

REFERENCE 6: 142:397729

REFERENCE 7: 142:367117

REFERENCE 8: 142:148256

REFERENCE 9: 142:107754

REFERENCE 10: 142:16877

L110 ANSWER 13 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **113427-24-0** REGISTRY
ED Entered STN: 19 Mar 1988
CN **1-165-Erythropoietin (human clone λHEPOFL13 protein moiety), glycoform α (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN EPO
CN Epoade
CN Epoetin alfa
CN Epogen
CN Eprex
CN Erypo
CN Erypo 4000
CN Espo
CN Procrit
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR US Adopted Names Council (USAN)
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CEN, CIN, DIOGENES, EMBASE,
IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*,
PATDPASPC, PHAR, PIRA, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Other Sources: WHO

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

306 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
306 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 143:133095

REFERENCE 2: 143:127065

REFERENCE 3: 143:127064

REFERENCE 4: 143:120713

REFERENCE 5: 143:72269

REFERENCE 6: 143:72188

REFERENCE 7: 143:71764

REFERENCE 8: 143:53890

REFERENCE 9: 143:53889

REFERENCE 10: 143:53882

L110 ANSWER 14 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **96024-34-9** REGISTRY
ED Entered STN: 28 Apr 1985
CN **Erythropoietin (human clone λHEPOFL13 protein moiety reduced) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 2: PN: EP1064951 SEQID: 2 unclaimed protein
CN 2: PN: WO0102017 SEQID: 2 claimed protein
CN 2: PN: WO0136489 SEQID: 2 claimed protein
CN 2: PN: WO0187329 SEQID: 2 claimed protein
CN **Erythropoietin (human 166-amino acid variant)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
LC STN Files: CA, CAPLUS, IMSPATENTS, IMSRESEARCH, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
24 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:11065

REFERENCE 2: 135:4473

REFERENCE 3: 134:105827

REFERENCE 4: 134:91083

REFERENCE 5: 133:38711

REFERENCE 6: 131:139951

REFERENCE 7: 131:73971

REFERENCE 8: 129:27012

REFERENCE 9: 128:320571

REFERENCE 10: 125:50111

L110 ANSWER 15 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **11096-26-7** REGISTRY
ED Entered STN: 16 Nov 1984
CN **Erythropoietin (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Ep
CN EPO
CN Epoetin
CN Epogis S
CN Hempoietine
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, PROUSDDR, RTECS*, SCISEARCH, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9386 REFERENCES IN FILE CA (1907 TO DATE)
286 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9410 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 143:152011

REFERENCE 2: 143:151887

REFERENCE 3: 143:151885

REFERENCE 4: 143:151210

REFERENCE 5: 143:150640

REFERENCE 6: 143:150628

REFERENCE 7: 143:147793

REFERENCE 8: 143:147789

REFERENCE 9: 143:147736

REFERENCE 10: 143:147566

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FILE 'WPIX' ENTERED AT 15:36:08 ON 23 AUG 2005
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FILE LAST UPDATED: 18 AUG 2005 <20050818/UP>
MOST RECENT DERWENT UPDATE: 200553 <200553/DW>
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http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
FOR DETAILS. <<<

=> d all abeq tech abex tot l131

L131 ANSWER 1 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2002-566640** [60] WPIX
DNC **C2002-160608**
TI Novel conjugate of **erythropoietin** glycoprotein with polyethylene glycol, useful for treating diseases correlated with anemia in chronic renal failure patients and acquired immunodeficiency syndrome.
DC A25 A96 B04 D16
IN BURG, J; ENGEL, A; FRANZE, R; HILGER, B; SCHURIG, H E; TISCHER, W; WOZNY, M; BURGERT, J; SHOKOUFANDEH, R
PA (HOFF) HOFFMANN LA ROCHE & CO AG F; (BURG-I) BURG J; (ENGE-I) ENGEL A; (FRAN-I) FRANZE R; (HILG-I) HILGER B; (SCHU-I) SCHURIG H E; (TISC-I) TISCHER W; (WOZN-I) WOZNY M
CYC 100
PI WO 2002049673 A2 20020627 (200260)* EN 40 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2002115833 A1 20020822 (200262) A61K038-22
AU 2002033230 A 20020701 (200264) A61K047-48 <--

EP 1345628 A2 20030924 (200363) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003074667 A 20030919 (200409) C07K014-505 <--
BR 2001016381 A 20040225 (200416) A61K047-48 <--
JP 2004525097 W 20040819 (200455) 68 C07K014-505 <--
MX 2003005406 A1 20031101 (200468) A61K047-48 <--
CN 1527726 A 20040908 (200478) A61K047-48 <--
ZA 2003004647 A 20041124 (200481) 55 A61K000-00

ADT WO 2002049673 A2 WO 2001-EP14434 20011208; US 2002115833 A1 US 2001-14363 20011211; AU 2002033230 A AU 2002-33230 20011208; EP 1345628 A2 EP 2001-984811 20011208, WO 2001-EP14434 20011208; KR 2003074667 A KR 2003-708299 20030619; BR 2001016381 A BR 2001-16381 20011208, WO 2001-EP14434 20011208; JP 2004525097 W WO 2001-EP14434 20011208, JP 2002-551010 20011208; MX 2003005406 A1 WO 2001-EP14434 20011208, MX 2003-5406 20030616; CN 1527726 A CN 2001-820609 20011208; ZA 2003004647 A ZA 2003-4647 20030613

FDT AU 2002033230 A Based on WO 2002049673; EP 1345628 A2 Based on WO 2002049673; BR 2001016381 A Based on WO 2002049673; JP 2004525097 W Based on WO 2002049673; MX 2003005406 A1 Based on WO 2002049673

PRAI EP 2000-127891 20001220

IC ICM A61K000-00; A61K038-22; **A61K047-48**; **C07K014-505**
ICS A61K038-18; A61P007-06; A61P013-12; A61P031-18; A61P035-00; C07K001-113; C07K014-575; C12P021-02

AB WO 200249673 A UPAB: 20021031

NOVELTY - A conjugate (I) comprising an **erythropoietin** (**EPO**) glycoprotein having an N-terminal alpha -amino group, chosen from human **EPO** (hEPO) or its analogs having sequence of hEPO modified by addition of 1-6 glycosylation sites or a rearrangement of a glycosylation site, where the glycoprotein is covalently linked to a poly(ethylene glycol) group, is new.

DETAILED DESCRIPTION - (I) comprises an **EPO** glycoprotein having an N-terminal alpha -amino group and in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, and chosen from hEPO or its analogs which have sequence of hEPO modified by addition of 1-6 glycosylation sites or a rearrangement of a glycosylation site, where the glycoprotein is covalently linked to a poly(ethylene glycol) group, with the -CO of the poly(ethylene glycol) group forming an amide bond with N-terminal alpha -amino group. The glycoprotein is covalently linked to a poly(ethylene glycol) group of formula (A).

-CO-(CH2)x -(OCH2CH2)m-OR (A)

R = methyl;
x = 2 or 3; and
m = 450-1350, 550-1000, preferably 650-750.

INDEPENDENT CLAIMS are also included for the following:
(1) a pharmaceutical composition (II) comprising (I);
(2) preparing (I);
(3) a conjugate prepared by the above method; and
(4) **EPO** glycoproteins comprising a sequence of 165 or 166 amino acids defined in the specification, having a N-terminal peptidic extension which represents a proteolytic cleavage site, optionally comprising a N-terminal purification tag.

ACTIVITY - Antianemic; anti-HIV; cytostatic.
No supporting data is given.

MECHANISM OF ACTION - None given.

USE - (I) Is useful for preparing medicaments for the treatment and prophylaxis of diseases correlated with anemia in chronic renal failure patients (CRF), acquired immunodeficiency syndrome (AIDS) and for treating cancer patients undergoing chemotherapy (claimed).

(I) Is useful for treating patients by stimulating the division and differentiation of committed erythroid progenitors in the bone marrow.

ADVANTAGE - (I) Has increased circulating half-life and plasma residence time, decreased clearance, increased clinical activity in vivo, improved potency, stability, and area under the curve when compared to unmodified **EPO**.

Dwg.0/5

FS CPI

FA AB; GI; DCN

MC CPI: **A05-H03**; A10-E01; A12-V01; **B04-C03C**; **B04-H07**; B04-H0700E; **B14-F03**; B14-G01; D05-H10; D05-H17A2

TECH UPTX: 20020919

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) Is prepared by expressing, preferably serum free fermenting recombinant **EPO** protein comprising a N-terminal peptidic extension which comprises a proteolytic cleavage sequence, protecting the epsilon-amino groups by citraconylation, proteolytic cleavage of the N-terminal peptidic extension, pegylating the N-terminal alpha-amino group with a compound of formula (B), deprotecting epsilon-amino group of the **EPO** glycoprotein, and optionally carrying out purification after each of the above steps. The recombinant **EPO** has a sequence of 165, 166, 174, 169 or 174 amino acids defined in the specification.

R = methyl;

x = 2 or 3; and

m = 450-1350, 550-1000, preferably 650-750.

Preferred Conjugate: (I) has the formula (C).

$CH3O(CH2CH2O)m-CH2CH2CH2CO-NH-P$ (C)

m = 650-750; and

P = a residue of the glycoprotein without the N-terminal alpha-amino group which forms an amide linkage with the poly(ethylene glycol) group.

The glycoprotein is a hEPO expressed by endogenous gene activation. The glycoprotein has the sequence of hEPO modified by a modification chosen from 22 modifications such as Asn30Thr32, Asn51Thr53, Asn57Thr59, Asn69 and Asn69Thr71, or preferably Gln24ser87Asn88Thr90, Gln38ser87Asn88Thr90 or Gln83ser87Asn88Thr90, or by a rearrangement comprising deletion of N-linked glycosylation sites in hEPO and addition of N-linked glycosylation site at position 88 of the sequence of hEPO.

ABEX UPTX: 20020919

ADMINISTRATION - Administered weekly once, at a dose of 0.01-10 mug/kg, preferably 0.1-3 mug/kg. Administration routes not specified.

EXAMPLE - The wild type **erythropoietin** (**EPO**) coding fragment was obtained. The coding fragment was amplified using primers **EPO**-EcoRI and **EPO**-SalI:

5'-GAGCCTGAATTCACCACC (**EPO**-EcoRI)

5'-AGGTGGGTCGACCTGGTCATCTGTCCCCTG (**EPO**-SalI)

The Polymerase Chain Reaction (PCR) fragment was digested and cloned into the multiple cloning site of the pre-digested pCI-dhfr vector fragment. Expression of **EPO** gene was under control of the human cytomegalovirus (CMV) immediate-early enhancer/promoter region, an optimized chimeric intron for regulated expression and SV40 late polyadenylation signal. Cloning of APPRIEGR-**EPO**, APP-**EPO** or APPGAAHY-**EPO** expression constructs were also performed. The mutagenized cell line Chinese Hamster ovary (CHO)/dhfr-(ATCC CRL-9096) deficient in the dhfr enzyme gene was obtained. Cells were transfected with **EPO** plasmids using the FuGENE6 transfection reagent. Transfected cells were selected in alpha-MEM lacking nucleosides (alpha-MEM), supplemented with 10% dialyzed fetal calf serum (FCS), and 2 mM glutamine. Single colonies were isolated by fluorescence activated cell sorting (FACS), expanded, and the culture supernatants were assayed for

production and secretion of **EPO**. The cells were transferred into glass spinner flasks and cultivated in a hydrogen carbonate-buffered medium in a humidified CO2 incubator. Typical serum free media was used for the inoculum preparation. After the initial growth period, the cell culture was diluted with fresh medium. After 3-5 days, the culture in the fermenter was used as inoculum for further fermentation. A batch refeed process was used, i.e. when the desired cell density was reached, 80% of the culture was harvested.
The determined harvest was centrifuged, and supernatant was filtered and collected in a second cooled vessel, and purified as described in WO9635718. The solution of the modified **EPO** was adjusted to pH 8.5-9 and stirred. Citraconic anhydride was added slowly to the solution in aliquots, pH of 9 was maintained and stirred. Residual citraconic anhydride was removed by adding 2 M ethanolamine solution. Cleavage of the modified protected **EPO** was achieved by adding cleavage protease or factor Xa. The removal of protease was achieved by size exclusion chromatography. The product was collected in fractions which were pooled according to the purity as analyzed by analytical reverse phase-high pressure liquid chromatography (rpHPLC).
The pooled fractions were concentrated to 7-8 mg/ml, and the pegylation reaction was performed at a molar ratio of 1:5 at a final protein concentration of 5 mg/ml. The pegylation reagent used was a methoxy-polyethylene glycol (PEG)-SBA. The 30 kDa PEG-SBA was dissolved in 1 mM HCl. Protected **EPO** was added and the reaction mixture was stirred. After 2 h, the reaction was stopped by adjusting the pH to 2.5 with acid. The separation of N-terminal pegylated **EPO** from excess reagents, reaction byproducts and non-pegylated **EPO** was achieved by chromatography. The product was collected in fractions which were pooled according to their purity as determined by high performance size exclusion chromatography. The PEG-A1 **EPO** was then concentrated to 4.5-7.5 mg/ml and stored frozen.

L131 ANSWER 2 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2002-463307** [49] WPIX
DNC **C2002-131715**
TI Polyethylene glycol-modified **erythropoietin** obtained by chemical modification to lysine residue at 52-position, for use in drug compositions to treat anemia, especially renal anemia.
DC A25 B04 D16
IN KAWATA, H; MACHIDA, M; MIYAMOTO, H; NAKAMURA, T; SEKIMORI, Y
PA (CHUS) CHUGAI SEIYAKU KK; (KAWA-I) KAWATA H; (MACH-I) MACHIDA M; (MIYA-I) MIYAMOTO H; (NAKA-I) NAKAMURA T; (SEKI-I) SEKIMORI Y
CYC 98
PI WO 2002032957 A1 20020425 (200249)* JA 46 C07K014-505 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001090312 A 20020429 (200255) C07K014-505 <--
EP 1333036 A1 20030806 (200353) EN C07K014-505 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2002536338 X 20040226 (200416) C07K014-505 <--
US 2004082765 A1 20040429 (200429) A61K038-24
ADT WO 2002032957 A1 WO 2001-JP8539 20010928; AU 2001090312 A AU 2001-90312 20010928; EP 1333036 A1 EP 2001-970285 20010928, WO 2001-JP8539 20010928; JP 2002536338 X WO 2001-JP8539 20010928, JP 2002-536338 20010928; US 2004082765 A1 WO 2001-JP8539 20010928, US 2003-399254 20030416

FDT AU 2001090312 A Based on WO 2002032957; EP 1333036 A1 Based on WO 2002032957; JP 2002536338 X Based on WO 2002032957
PRAI JP 2000-315421 20001016
IC ICM A61K038-24; **C07K014-505**
ICS A61K038-22; A61K038-32; A61K047-34; **A61K047-48**; A61P007-06; A61P043-00; C07K014-23
AB WO 200232957 A UPAB: 20020802
NOVELTY - A mono-polyethylene glycol-modified **erythropoietin** (PEG-modified **EPO**) produced by chemically modifying natural **EPO** with PEG, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) mono-PEG-modified **EPO** compositions containing the mono-PEG-modified **EPO** and/or a PEG-modified **EPO** of natural **EPO** with 2 or more amino acid residues modified by PEG, 1 molecule of which as determined by gel filtration column chromatography in an aqueous solvent system has an apparent molecular weight of 100-900 kDa;
(2) **EPO** preparations with long-lasting drug effect containing the PEG-modified **EPO** as active ingredient; and
(3) preparing the PEG-modified **EPO** compositions by reacting natural **EPO** with the succcinimidyl ester derivative of PEG.
ACTIVITY - Antianemic.
MECHANISM OF ACTION - None given in source material.
USE - The modified **EPO** is for use in drug compositions to treat anemia especially renal anemia.
ADVANTAGE - The **EPO** has enhanced and high long-lasting drug effect but without damage to its physiological activity, which is obtainable by introducing PEG into a controlled binding site at a controlled number of binding molecules. With the formulated drug compositions agents, less nursing and treatment time is needed, less pain and cost to patients too.
DESCRIPTION OF DRAWING(S) - Mapped chromatographic pattern by liquid chromatography after digestion of mono-mPEG-**EPO** with endoprotease Lys-C: with axes of PEG binding site fixation of PEG(1)-**EPO** vs. intact **EPO**(x)(-0.5). (Drawing includes non-English language text).
Dwg.2/14
FS CPI
FA AB; GI; DCN
MC CPI: A10-E01; A12-V01; **B04-C03C**; **B04-H07**; **B14-F03**; B14-N10; D05-H10
TECH UPTX: 20020802
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Modified **EPO**: Chemical modification with PEG is at the lysine residue at 52-position of natural **EPO**. A mono-PEG-modified **EPO** is obtained by modifying natural **EPO** with a PEG having a molecular weight of 5-40 kDa, one molecule of which as determined by gel filtration column chromatography in an aqueous solvent system has an apparent molecular weight of 100-900 kDa.
ABEX UPTX: 20020802
ADMINISTRATION - Administration is non-oral, e.g. intranasal or by injection at 5-50 microg.

EXAMPLE - A 0.5-ml solution of rh **erythropoietin** (**EPO**) (2.94 mg/ml) in 0.1 mM phosphate buffer at pH 8 was stirred with methoxy polyethylene glycol (PEG)-SPA (succinimidyl propionate; molecular weight of 20 kDa; 3.97 molar ratio), at room temperature for 30 minutes. Then, 10% 0.1 M glycine solution was added to deactivate the ester. After work-up and purification by chromatography on Superdex 200 HR10/30 (RTM),

3.8 mg mono-mPEG-**EPO** and 1.6 mg di-mPEG-**EPO** were obtained.

L131 ANSWER 3 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2002-097323** [13] WPIX
DNC **C2002-030219**
TI Novel **erythropoietin** stimulating protein modified by conjugation to a polyethylene glycol moiety has a longer half life than the unmodified form and is useful to treat hematopoietic disorders.
DC A25 A96 B04
IN BOONE, T C; FREEMAN, A; GEGG, C V; KINSTLER, O B; BOONE, T; GEGG, C; KINSTLER, O
PA (AMGE-N) AMGEN INC
CYC 96
PI WO 2001076640 A2 20011018 (200213)* EN 27 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001055256 A 20011023 (200213) A61K047-48 <--
EP 1267942 A2 20030102 (200310) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 6586398 B1 20030701 (200345) A61K038-00
US 2003166566 A1 20030904 (200359) A61K038-22
JP 2003530361 W 20031014 (200368) 58 A61K047-48 <--
MX 2002009896 A1 20030301 (200413) A61K047-48 <--
ADT WO 2001076640 A2 WO 2001-US11346 20010406; AU 2001055256 A AU 2001-55256 20010406; EP 1267942 A2 EP 2001-928395 20010406, WO 2001-US11346 20010406; US 6586398 B1 US 2000-545335 20000407; US 2003166566 A1 Cont of US 2000-545335 20000407, US 2003-409807 20030407; JP 2003530361 W JP 2001-574155 20010406, WO 2001-US11346 20010406; MX 2002009896 A1 WO 2001-US11346 20010406, MX 2002-9896 20021007
FDT AU 2001055256 A Based on WO 2001076640; EP 1267942 A2 Based on WO 2001076640; US 2003166566 A1 Cont of US 6586398; JP 2003530361 W Based on WO 2001076640; MX 2002009896 A1 Based on WO 2001076640
PRAI US 2000-545335 20000407; US 2003-409807 20030407
IC ICM A61K038-00; A61K038-22; **A61K047-48**
ICS A61K038-18; A61P007-06; C07K017-00; C08G063-48; C08G063-91
AB WO 200176640 A UPAB: 20020226
NOVELTY - A substantially homogenous preparation of chemically modified novel **erythropoietin** stimulating protein (NESP) is new.
ACTIVITY - anti-anemia
MECHANISM OF ACTION - increases erythropoiesis
USE - The chemically modified NESP is used to treat a hematopoietic disorder (claimed).
ADVANTAGE - The PEGylated NESP has a longer half life and so needs to be administered less frequently than prior art treatment with NESP or **rHuEPO.**
DESCRIPTION OF DRAWING(S) - Hemoglobin response of normal mice after single bolus injections of 30 mu g/kg 30kD mono-PEG:NESP conjugate (closed triangle), 20kD mono-PEG:NESP conjugate (closed square), 5-kD poly-PEG:NESP conjugate (closed circle) or unmodified NESP (open circle) 5-17 days post treatment.
Dwg.21/22
FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; B04-C03D; B04-N02; **B14-F01**

TECH UPTX: 20020226
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred preparation: The NESP is preferably chemically modified with dextran, poly(n-vinyl pyurrolidone), a polyethylene glycol (PEG), a propropylene glycol homopolymer, a polypropylene oxide/ethylene oxide co-polymer, a polyoxyethylated polyol or a polyvinyl alcohol, more preferably with PEG with a molecular weight of 2-100kD, more preferably 5-30kD. The preparation may be a mixture of mono-PEGylated and poly-PEGylated NESP and is preferably comprised of at least 95% N-terminally mono-PEGylated NESP and at most 5% unPEGylated NESP. The NESP preferably has the 165 amino acid sequence fully defined in the specification. The PEG moiety is connected to NESP through aldehydes generated in the NESP carbohydrate chains or using methoxy-PEG-NHS chemistry.

ABEX UPTX: 20020226
ADMINISTRATION - Administration is by intraperitoneal, subcutaneous or intramuscular injection, preferably with iron to maintain increased erythropoiesis. Dosage frequency is once every 4-6 weeks.
EXAMPLE - 30kD mono-PEG:NESP derived by acylation with the 30kD PEG-NHS ester, 20Kd mono-PEG:NESP or 5kD polyPEG:NESP derived by reductive alkylation with the 20kD and 5kD PEG-aldehyde, or unmodified NESP respectively were administered to normal mice as a single bolus subcutaneous dose at 30, 10 or 3 mug/kg. The erythropoietic response and duration was monitored as reticulocyte count or hemoglobin concentration over time. The data showed that all three forms induced a strong erythropoietic response with significant dose reduction, and a prolonged efficacy relative to the unmodified NESP (see figure).

L131 ANSWER 4 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2001-147051** [15] WPIX
DNC **C2001-043438**
TI Novel **erythropoietin**-glycoprotein conjugate useful for treating diseases correlated with anemia in chronic renal failure patients, AIDS and for treating cancer, is linked to polyethylene glycol through linker.
DC A96 B04
IN BURG, J; HILGER, B; JOSEL, H
PA (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE DIAGNOSTICS GMBH
CYC 90
PI WO 2001002017 A2 20010111 (200115)* EN 40 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000064299 A 20010122 (200125) A61K047-48 <--
US 6340742 B1 20020122 (200208) A61K038-18
NO 2001006304 A 20020219 (200223) A61K047-48 <--
EP 1196443 A2 20020417 (200233) EN C07K014-505 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 2000012138 A 20020507 (200238) A61K047-48 <--
KR 2002026514 A 20020410 (200267) C07K014-505 <--
CN 1359392 A 20020717 (200268) C07K014-505 <--
HU 2002001971 A2 20020930 (200272) C07K014-505 <--
CZ 2001004682 A3 20021113 (200282) A61K047-48 <--
JP 2003503464 W 20030128 (200309) 51 A61K038-22
ZA 2001010097 A 20030528 (200341) 54 C07K000-00
MX 2001012974 A1 20020801 (200367) A61K047-48 <--
AU 768452 B 20031211 (200404) A61K047-48 <--
NZ 516170 A 20040227 (200418) A61K047-48 <--

EP 1196443 B1 20040526 (200435) EN C07K014-505 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI
DE 60011087 E 20040701 (200443) C07K014-505 <--
RU 2232163 C2 20040710 (200455) C07K014-505 <--
ES 2220501 T3 20041216 (200506) C07K014-505 <--
DE 60011087 T2 20050616 (200540) C07K014-505 <--
IN 2001001842 P4 20050304 (200547) EN C07K014-505 <--

ADT WO 2001002017 A2 WO 2000-EP6009 20000628; AU 2000064299 A AU 2000-64299 20000628; US 6340742 B1 Provisional US 1999-142243P 19990702, Provisional US 1999-147452P 19990805, Provisional US 1999-151454P 19990830, US 2000-604871 20000628; NO 2001006304 A WO 2000-EP6009 20000628, NO 2001-6304 20011221; EP 1196443 A2 EP 2000-951312 20000628, WO 2000-EP6009 20000628; BR 2000012138 A BR 2000-12138 20000628, WO 2000-EP6009 20000628; KR 2002026514 A KR 2002-700029 20020102; CN 1359392 A CN 2000-809895 20000628; HU 2002001971 A2 WO 2000-EP6009 20000628, HU 2002-1971 20000628; CZ 2001004682 A3 WO 2000-EP6009 20000628, CZ 2001-4682 20000628; JP 2003503464 W WO 2000-EP6009 20000628, JP 2001-507507 20000628; ZA 2001010097 A ZA 2001-10097 20011207; MX 2001012974 A1 WO 2000-EP6009 20000628, MX 2001-12974 20011214; AU 768452 B AU 2000-64299 20000628; NZ 516170 A NZ 2000-516170 20000628, WO 2000-EP6009 20000628; EP 1196443 B1 EP 2000-951312 20000628, WO 2000-EP6009 20000628; DE 60011087 E DE 2000-00011087 20000628, EP 2000-951312 20000628, WO 2000-EP6009 20000628; RU 2232163 C2 WO 2000-EP6009 20000628, RU 2002-102232 20000628; ES 2220501 T3 EP 2000-951312 20000628; DE 60011087 T2 DE 2000-00011087 20000628, EP 2000-951312 20000628, WO 2000-EP6009 20000628; IN 2001001842 P4 IN 2001-CN1842 20011231, WO 2000-EP6009

FDT AU 2000064299 A Based on WO 2001002017; EP 1196443 A2 Based on WO 2001002017; BR 2000012138 A Based on WO 2001002017; HU 2002001971 A2 Based on WO 2001002017; CZ 2001004682 A3 Based on WO 2001002017; JP 2003503464 W Based on WO 2001002017; MX 2001012974 A1 Based on WO 2001002017; AU 768452 B Previous Publ. AU 2000064299, Based on WO 2001002017; NZ 516170 A Based on WO 2001002017; EP 1196443 B1 Based on WO 2001002017; DE 60011087 E Based on EP 1196443, Based on WO 2001002017; RU 2232163 C2 Based on WO 2001002017; ES 2220501 T3 Based on EP 1196443; DE 60011087 T2 Based on EP 1196443, Based on WO 2001002017

PRAI US 1999-151454P 19990830; US 1999-142243P 19990702; US 1999-147452P 19990805; US 2000-604871 20000628

IC ICM A61K038-18; A61K038-22; **A61K047-48**; C07K000-00; **C07K014-505**
ICS A61P007-06; A61P013-12; A61P031-18; A61P035-00

AB WO 200102017 A UPAB: 20010317
NOVELTY - A conjugate (I) comprising, human **erythropoietin** glycoprotein (**EPO**) having at least one free amino group and having in vivo biological activity of causing bone marrow cells to increase the production of reticulocytes and red blood cells, or its analogs, covalently linked to 1-3 lower-alkoxy poly(ethylene glycol) groups through a linker (L), is new.

DETAILED DESCRIPTION - (I) comprises **EPO** or its analog having primary structure of human **erythropoietin** modified by the addition of 1-6 glycosylation sites or by the rearrangement of at least one glycosylation site. The glycoprotein is covalently linked to 1-3 lower-alkoxy poly(ethylene glycol) groups, through a linker of formula -C(O)-X-S-Y', with C(O) of the linker forming an amide bond with the free amino groups of glycoprotein.

X = -(CH2)k- or -CH2(O-CH2-CH2)k-;
k = 1-10; and

Y' = (CH2)2-SO2-(CH2)2, CH2C(O)NH(CH2)2 or a group of formula (i) or (ii).

The average molecular weight of each (PEG) moiety is 20-40

kilodaltons, and molecular weight of (I) is from 51-175 kilodaltons.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising 1-90 % of (I);

(2) a pharmaceutical composition comprising (I) or (II);

(3) preparing (I) or (II) by covalent linking of thiol groups to an **EPO**, and coupling the resulting activated **EPO** with PEG derivative; and

(4) (I) or (II) prepared by the above said method.

ACTIVITY - Antianemic; anti-HIV; cytostatic.

MECHANISM OF ACTION - Enhancer of production of reticulocytes and red blood cells.

Normal healthy mice, 7-15 weeks old, were administered subcutaneously with 0.2 ml of methoxy-PEG-maleimide coupled to **EPO**, unmodified **EPO** and buffer solution. Over a period of 4 days starting 72 hours after the administration, blood was drawn by puncture of the tail vein, diluted and stained with acridine orange staining solution for 3-10 minutes. The reticulocytes were counted. The results showed superior activity and prolonged half life of the pegylated **EPO** species indicated by the significantly increased amounts of reticulocytes and shift of the reticulocytes count maximum using the same dose per mouse.

USE - (I) and (II) are useful for preparation of medicaments for the treatment of prophylaxis of disease correlated with anemia in chronic renal failure patients (CRF), AIDS and for the treatment of cancer patients undergoing chemotherapy. (I) and (II) are also useful for treating the above said diseases (claimed).

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: A10-E; A10-E08A; A12-V01; A12-W11L; **B04-C03C**; **B04-H07**; B04-N06; B14-A02B1; **B14-F03**; B14-H01B

TECH UPTX: 20010317

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Compound: (I) is of formula P'-(NH-CO-X-S-Y'-(OCH2CH2)m-OR)n.

m = 450-900;

n = 1-3;

R = lower alkyl; and

P' = **EPO** without amino group or amino group which form an amide linkage with X.

P' is also preferably of formula F1 or F2.

X = (CH2)k (preferably CH2);

k = 1-4;

m = 550-800 (preferably 650-700);

n = 1; and

R = CH3.

The average molecular weight of PEG is 24-35, preferably 30 kilodaltons. The glycoprotein is covalently linked to 1 or 2 lower alkoxy e.g. methoxy, capped PEG moieties. **EPO** is expressed by endogenous gene activation. Glycoprotein of **EPO** is modified by N30T32, N51T53, N57T59, N69, N69T71, S68N69T71, V87N88T90, S87N88T90, S87N88G89T90, S87N88T90T92, S87N88T90A162, N69T71S87N88T90, N30T32V87N88T90, N89I90T91, S87N89I90T91, N136T138, N138T140, T125 or P124T125. The glycoprotein has a sequence comprising human **EPO**, and a second sequence at the carboxy terminus of **EPO**, containing at least one glycosylation site. The second sequence comprises a sequence derived from carboxy terminal sequence of human chorionic gonadotropin. The glycoprotein has a sequence SSSSKAPPPSLPSPSRLPGPSDTPILPQ, or a sequence modified by S87N88T90 or N30T32V87N88T90. The glycoprotein has the sequence of **EPO** modified by rearrangement of glycosylation site, preferably deletion of any of the N-linked carbohydrate sites in **EPO** or addition of N-linked carbohydrate site at position 88 of **EPO**. The

glycoprotein has a sequence Q24S87N88T90, Q38S87N88T90, or Q83S87N88T90. Percentage of (I) in (II) is 1-90, preferably 1-96 %.

ABEX UPTX: 20010317

SPECIFIC SEQUENCES - **EPO** comprises a sequence of 165 or 166 amino acids fully defined in the specification. The glycoprotein has a sequence SSSSKAPPPSLPSPSRLPGPSDTPILPQ (claimed).

ADMINISTRATION - 0.01-10 (preferably 0.1-1) mug/kg of (I), containing 10-1000 (preferably 50-400) mug/ml of **erythropoietin** is administered by subcutaneous or intravenous injection.

EXAMPLE - 100 mg **erythropoietin** glycoprotein (**EPO**) was activated with SATA. The resulting activated **EPO** carrying covalently linked blocked thiol groups was separated from by-products like N-hydroxy-succinimide or non-reacted SATA by dialysis. 380 mg methoxy-PEG-maleimide was dissolved in the solution containing 95 mg activated **EPO.** The resulting molar ratio between activated **EPO** and methoxy-PEG-maleimide in the solution was 1:4. Covalently linked blocked thiol groups of activated **EPO** were de-blocked by 1 M aqueous hydroxylamine solution ad 30 mM. The resulting activated **EPO** in the reaction mixture of the solution contained free thiol (-SH) groups. Deblocking of the thiol groups was followed immediately by coupling between the activated **EPO** and methoxy-PEG-maleimide for 90 minutes, and 0.2 M aqueous cysteine solution ad 2 mM was added to stop coupling. After 30 minutes excess free thiol groups of the activated **EPO** were blocked by addition of a 0.5 M N-methylmaleimide solution in DMSO to reach a concentration of 5 mM. After 30 minutes the resulting reaction mixture now containing pegylated **EPO** species was dialyzed and purified. Content and purity of tri-, di- and mono-pegylated **EPO** species were evaluated on Coomassie-stained SDS-PAA gels.

L131 ANSWER 5 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2001-135308** [14] WPIX
DNC **C2001-057629**
TI New conjugate having modified **erythropoietin** glycoprotein useful for stimulating red blood cell production and for treating diseases correlated with anemia in chronic renal failure, AIDS or cancer patients.
DC A96 B04
IN BAILON, P S; SEBASTIAN BAILON, P
PA (HOFF) HOFFMANN LA ROCHE & CO AG F; (BAIL-I) BAILON P S; (HOFF) HOFFMANN LA ROCHE INC
CYC 40
PI

NO	2000003372	A	20010103	(200114)*		C07K017-10	
CA	2310536	A1	20010102	(200114) EN		C07K014-505	<--
DE	10031839	A1	20010201	(200114)		C07K014-505	<--
GB	2353281	A	20010221	(200115)		C07K017-08	
JP	2001064300	A	20010313	(200118)	16	C07K014-505	<--
EP	1064951	A2	20010103	(200120)B EN	16	A61K047-48	<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI							
ZA	2000003282	A	20010328	(200121)	31	A61K000-00	
FR	2795734	A1	20010105	(200124)		C07K014-505	<--
HU	2000002553	A2	20010328	(200124)		C12P021-02	
AU	2000042744	A	20010104	(200128)		C07K014-575	
CN	1280137	A	20010117	(200128)		C07K014-505	<--
AU	736067	B	20010726	(200149)		C07K014-575	
KR	2001049676	A	20010615	(200171)		C07K014-505	<--
BR	2000002276	A	20011211	(200203)		A61K038-42	
NZ	505454	A	20011221	(200210)		C07K017-08	
CZ	2000002386	A3	20020417	(200231)		A61K047-48	<--

SK 2000000987	A3	20020604	(200247)		A61K047-48	<--
SG 92717	A1	20021119	(200303)		C07K014-575	
US 6583272	B1	20030624	(200343)		C07K014-505	<--
US 2003120045	A1	20030626	(200343)		C07K014-575	
ES 2191511	A1	20030901	(200363)		A61K047-48	<--
IT 1318606	B	20030827	(200374)		A61K000-00	
GB 2393960	A	20040414	(200433)		C07K017-08	
JP 2004155787	A	20040603	(200436)	23	C07K014-505	<--
GB 2353281	B	20040609	(200438)		C07K017-08	
GB 2393960	B	20040804	(200451)		C07K017-08	
CN 1515590	A	20040728	(200469)		C07K017-02	
IL 137056	A	20041124	(200504)		C07K014-505	<--
ES 2191511	B1	20050101	(200505)		A61K047-48	<--

ADT NO 2000003372 A NO 2000-3372 20000628; CA 2310536 A1 CA 2000-2310536 20000628; DE 10031839 A1 DE 2000-10031839 20000630; GB 2353281 A GB 2000-16205 20000630; JP 2001064300 A JP 2000-201525 20000703; EP 1064951 A2 EP 2000-113115 20000628; ZA 2000003282 A ZA 2000-3282 20000629; FR 2795734 A1 FR 2000-8609 20000703; HU 2000002553 A2 HU 2000-2553 20000630; AU 2000042744 A AU 2000-42744 20000628; CN 1280137 A CN 2000-107889 20000629; AU 736067 B AU 2000-42744 20000628; KR 2001049676 A KR 2000-36976 20000630; BR 2000002276 A BR 2000-2276 20000703; NZ 505454 A NZ 2000-505454 20000628; CZ 2000002386 A3 CZ 2000-2386 20000623; SK 2000000987 A3 SK 2000-987 20000627; SG 92717 A1 SG 2000-3658 20000629; US 6583272 B1 Provisional US 1999-142254P 19990702, Provisional US 1999-150225P 19990823, Provisional US 1999-151548P 19990831, Provisional US 1999-166151P 19991117, US 2000-604938 20000627; US 2003120045 A1 Provisional US 1999-142254P 19990702, Provisional US 1999-150225P 19990823, Provisional US 1999-151548P 19990831, Provisional US 1999-166151P 19991117, Cont of US 2000-604938 20000627, US 2002-293551 20021114; ES 2191511 A1 ES 2000-1625 20000630; IT 1318606 B IT 2000-MI1479 20000630; GB 2393960 A Div ex GB 2000-16205 20000630, GB 2004-86 20040105; JP 2004155787 A Div ex JP 2000-201525 20000703, JP 2003-419520 20031217; GB 2353281 B GB 2000-16205 20000630; GB 2393960 B Div ex GB 2000-16205 20000630, GB 2004-86 20040105; CN 1515590 A Div ex CN 2000-107889 20000629, CN 2004-3602 20000629; IL 137056 A IL 2000-137056 20000628; ES 2191511 B1 ES 2000-1625 20000630

FDT AU 736067 B Previous Publ. AU 2000042744

PRAI US 1999-166151P 19991117; US 1999-142254P 19990702;
US 1999-150225P 19990823; US 1999-151548P 19990831;
US 2000-604938 20000627; US 2002-293551 20021114

IC ICM A61K000-00; A61K038-42; **A61K047-48**; **C07K014-505**; C07K014-575; C07K017-02; C07K017-08; C07K017-10; C12P021-02
ICS A61K038-17; A61K038-18; A61K038-22; A61K039-00; A61P007-00; A61P007-06; A61P013-12; A61P031-00; A61P031-18; A61P035-00; C07H000-00; C07K001-107; C07K014-59; C07K017-00; C07K019-00; C08G065-00; C12N015-12

AB EP 1064951 A UPAB: 20010410 ABEQ treated as Basic

NOVELTY - A conjugate comprising an **erythropoietin** (**EPO**) glycoprotein is new. The **EPO** has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

DETAILED DESCRIPTION - A conjugate comprising an **erythropoietin** (**EPO**) glycoprotein is new. The **EPO** has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

The **EPO** comprises human **EPO** (hEPO) or its analogs, which has the sequence of hEPO modified by the addition of 1-6

glycosylation sites or a rearrangement of at least one glycosylation site.

The glycoprotein is covalently linked to n polyethylene glycol groups of formula CO-(CH2)x-(OCH2CH2)m-OR (I).

R = lower alkyl;
x = 2 or 3;
m = 450-900 and
n = 1-3.

n And m are chosen so that the molecular weight of the conjugate minus the **erythropoietin** glycoprotein is 20-100 kilodaltons. The CO of each polyethylene glycol group forms an amide bond with one of the amino groups.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising conjugates, each of the conjugates comprising the **erythropoietin** glycoprotein described above, the percentage of conjugates (where n =1) is at least 90% and

(2) preparation of (I).

ACTIVITY - Antianemic; immunostimulant; cytostatic; nephrotropic.

MECHANISM OF ACTION - Bone marrow cell stimulator; erythroid progenitor stimulator.

In separate experiments, a single dose of unmodified **EPO** (25 ng of **EPO**), PEG(SBA)-**EPO** mixture (10 ng of conjugate), mono- and di-pegylated **EPOs** (10 ng conjugate), PEG(SPA)-**EPO** (10 ng of conjugate) and buffer solution were administered to mice. The results showed the superior activity and the prolonged half life of the pegylated **EPO** species indicated by the increased amounts of reticulocytes and the shift of the reticulocytes count maximum using the same dose per mouse (10 ng), compared to a dose of 25 ng for unmodified **EPO**. At 96 h, the amount of reticulocytes for unmodified **EPO**, 30 kDa PEG(SPA)-**EPO**, mono-SBA-**EPO**, di-SBA-**EPO**, PEG-**EPO** conjugate mixture and the control buffer were 500, 1406, 1501, 926, 1338 and 697, respectively. At 144 hours, the number of reticulocytes were approx. 0, 535, 607, 665, 660 and 708, respectively.

USE - Useful for the treating or preventing diseases correlated with anemia in chronic renal failure, AIDS or cancer patients undergoing chemotherapy. The conjugate or composition is also useful for preparing medicaments for the treatment or prophylaxis of these diseases (all claimed).

ADVANTAGE - Compared to unmodified **EPO** and conventional PEG-**EPO** conjugates, the conjugates have an increased circulating half-life and plasma residence time, decreased clearance, and increased clinical activity in vivo.

Dwg.0/0

AB NO 200003372 A UPAB: 20010418

NOVELTY - A conjugate comprising an **erythropoietin** (**EPO**) glycoprotein is new. The **EPO** has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

DETAILED DESCRIPTION - A conjugate comprising an **erythropoietin** (**EPO**) glycoprotein is new. The **EPO** has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

The **EPO** comprises human **EPO** (hEPO) or its analogs, which has the sequence of hEPO modified by the addition of 1-6 glycosylation sites or a rearrangement of at least one glycosylation site.

The glycoprotein is covalently linked to n polyethylene glycol groups of formula CO-(CH2)x-(OCH2CH2)m-OR (I).

R = lower alkyl;
x = 2 or 3;
m = 450-900 and
n = 1-3.

n And m are chosen so that the molecular weight of the conjugate minus the **erythropoietin** glycoprotein is 20-100 kilodaltons. The CO of each polyethylene glycol group forms an amide bond with one of the amino groups.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising conjugates, each of the conjugates comprising the **erythropoietin** glycoprotein described above, the percentage of conjugates (where n =1) is at least 90% and

(2) preparation of (I).

ACTIVITY - Antianemic; immunostimulant; cytostatic; nephrotropic.

MECHANISM OF ACTION - Bone marrow cell stimulator; erythroid progenitor stimulator.

In separate experiments, a single dose of unmodified **EPO** (25 ng of **EPO**), PEG(SBA)-**EPO** mixture (10 ng of conjugate), mono- and di-pegylated **EPOs** (10 ng conjugate), PEG(SPA)-**EPO** (10 ng of conjugate) and buffer solution were administered to mice. The results showed the superior activity and the prolonged half life of the pegylated **EPO** species indicated by the increased amounts of reticulocytes and the shift of the reticulocytes count maximum using the same dose per mouse (10 ng), compared to a dose of 25 ng for unmodified **EPO**. At 96 h, the amount of reticulocytes for unmodified **EPO**, 30 kDa PEG(SPA)-**EPO**, mono-SBA-**EPO**, di-SBA-**EPO**, PEG-**EPO** conjugate mixture and the control buffer were 500, 1406, 1501, 926, 1338 and 697, respectively. At 144 hours, the number of reticulocytes were approx. 0, 535, 607, 665, 660 and 708, respectively.

USE - Useful for the treating or preventing diseases correlated with anemia in chronic renal failure, AIDS or cancer patients undergoing chemotherapy. The conjugate or composition is also useful for preparing medicaments for the treatment or prophylaxis of these diseases (all claimed).

ADVANTAGE - Compared to unmodified **EPO** and conventional PEG-**EPO** conjugates, the conjugates have an increased circulating half-life and plasma residence time, decreased clearance, and increased clinical activity in vivo.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: A10-E08B; A12-V01; **B04-C03C**; **B04-H07**; **B14-F04**; B14-G01B

ABEQ EP 1064951 A UPAB: 20010410

NOVELTY - A conjugate comprising an **erythropoietin** (**EPO**) glycoprotein is new. The **EPO** has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

DETAILED DESCRIPTION - A conjugate comprising an **erythropoietin** (**EPO**) glycoprotein is new. The **EPO** has at least one free amino group and has the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells. The glycoprotein is covalently linked to polyethylene glycol groups.

The **EPO** comprises human **EPO** (hEPO) or its analogs, which has the sequence of hEPO modified by the addition of 1-6 glycosylation sites or a rearrangement of at least one glycosylation site.

The glycoprotein is covalently linked to n polyethylene glycol groups

of formula CO-(CH2)x-(OCH2CH2)m-OR (I).
R = lower alkyl;
x = 2 or 3;
m = 450-900 and
n = 1-3.

n And m are chosen so that the molecular weight of the conjugate minus the **erythropoietin** glycoprotein is 20-100 kilodaltons. The CO of each polyethylene glycol group forms an amide bond with one of the amino groups.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising conjugates, each of the conjugates comprising the **erythropoietin** glycoprotein described above, the percentage of conjugates (where n =1) is at least 90% and

(2) preparation of (I).

ACTIVITY - Antianemic; immunostimulant; cytostatic; nephrotropic.

MECHANISM OF ACTION - Bone marrow cell stimulator; erythroid progenitor stimulator.

In separate experiments, a single dose of unmodified **EPO** (25 ng of **EPO**), PEG(SBA)-**EPO** mixture (10 ng of conjugate), mono- and di-pegylated **EPOs** (10 ng conjugate), PEG(SPA)-**EPO** (10 ng of conjugate) and buffer solution were administered to mice. The results showed the superior activity and the prolonged half life of the pegylated **EPO** species indicated by the increased amounts of reticulocytes and the shift of the reticulocytes count maximum using the same dose per mouse (10 ng), compared to a dose of 25 ng for unmodified **EPO**. At 96 h, the amount of reticulocytes for unmodified **EPO**, 30 kDa PEG(SPA)-**EPO**, mono-SBA-**EPO**, di-SBA-**EPO**, PEG-**EPO** conjugate mixture and the control buffer were 500, 1406, 1501, 926, 1338 and 697, respectively. At 144 hours, the number of reticulocytes were approx. 0, 535, 607, 665, 660 and 708, respectively.

USE - Useful for the treating or preventing diseases correlated with anemia in chronic renal failure, AIDS or cancer patients undergoing chemotherapy. The conjugate or composition is also useful for preparing medicaments for the treatment or prophylaxis of these diseases (all claimed).

ADVANTAGE - Compared to unmodified **EPO** and conventional PEG-**EPO** conjugates, the conjugates have an increased circulating half-life and plasma residence time, decreased clearance, and increased clinical activity in vivo.

Dwg.0/0

TECH UPTX: 20010410

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises condensing a polymeric compound of formula (II) with a **EPO** glycoprotein.

Preferred compounds: The conjugate is of formula (IA) or (IB).
P = the residue of the glycoprotein without the n amino group(s), which form amide linkage(s) with the polyethylene glycol group(s);
R = methyl;
m = 650-750 and
n = 1.

The glycoprotein is preferably hEPO, where the hEPO glycoprotein is expressed by endogenous gene activation. The glycoprotein has a sequence comprising 165 amino acids defined in the specification. The glycoprotein has the hEPO sequence, which has a modification selected from the following: Asn30Thr32; Asn51Thr53; Asn57Thr59; Asn69; Asn69Thr71; Ser68Asn69Thr71; Val87Asn88Thr90; Ser87Asn88Thr90; Ser87Asn88Gly89Thr90; Ser87Asn88Thr90Thr92; Ser87Asn88Thr90Ala162; Asn69Thr71Ser87Asn88Thr90; Asn30Thr32Val87Asn88Thr90; Asn89Ile90Thr91; Ser87Asn89Ile90Thr91; Asn136Thr138; Asn138Thr140; Thr125 or Pro124Thr125.

The glycoprotein also has a sequence comprising the hEPO sequence and a second sequence at the carboxy terminus of the human **erythropoietin** sequence, where the second sequence contains at least one glycosylation site. The second sequence comprises a sequences derived from the carboxy terminal sequence of the human chorionic gonadotropin. The glycoprotein has a sequence selected from:
(a) the sequence hEPO and the defined 28-amino acid sequence at the carboxy terminus of the hEPO sequence;
(b) the sequence in (a) modified by Ser87Asn88Thr90; or
(c) the sequence in (a) modified by Asn30Thr32Val87Asn88Thr90.
The glycoprotein also has the hEPO sequence modified by a rearrangement of at least one glycosylation site, where the rearrangement comprises deletion of any of the N-linked glycosylation sites in human **erythropoietin** and addition of an N-linked glycosylation site at position 88 of the hEPO sequence. In particular, the hEPO has a modification selected from: Gln24Ser87Asn88Thr90; Gln38Ser87Asn88Thr90; or Gln83Ser87Asn88Thr90.
Preferred composition: The percentage of conjugates in the composition, where n = 1, is at least 92%, preferably 96%.

ABEX UPTX: 20010410

ADMINISTRATION - The dosage is 0.01-10 (preferably 0.1-1) mug/kg administered once weekly.

EXAMPLE - **Erythropoietin** (**EPO**)-producing CHO cell line (ATCC CRL8695) was prepared. A batch re-feed process was used, i.e. when the desired cell density was reached, 80% of the culture was harvested. The remaining culture was replenished with fresh culture medium and cultivated until the next harvest. The cells were removed by centrifugation or filtration and discarded. The **EPO** containing supernatant was in-line filtered, collected and purified. The purification of **EPO**-protein was disclosed in WO96/35718. The purified **EPO** was subjected to pegylation with mPEG-SBA (II: R = Me; x = 0-3 and m = 650-750)
To 100 mg of EPOsf (9.71 ml of a 10.3 mg/ml EPOsf stock, 5.48 micro-mol), 10 ml of 0.1 M potassium phosphate buffer (pH 7.5) containing 506 mg of 30 kDa methoxy-PEG-SBA (16.5 micro-mol) was added and mixed for 2 hours at room temperature (20-23degreesC). The final protein concentration was 5 mg/ml and the protein:PEG reagent ratio was 1:3. After 2 hours, the reaction was stopped by adjusting the pH to 4.5 with glacial acetic acid and stored at -20degreesC, until ready for purification. The conjugate mixture was purified, then analyzed by SDS-PAGE, and the degree of pegylation determined. The purified conjugate mixture comprised of mono- and di-PEG-EPOsf and was free of unmodified EPOsf as determined by SDS-PAGE analysis. Conjugate mixture comprised 23.4 mg or 78% of the starting material.

=> d his

(FILE 'HOME' ENTERED AT 14:19:58 ON 23 AUG 2005)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 14:20:07 ON 23 AUG 2005
L1 1 S US20040209802/PN OR (US2003-706701# OR EP2002-26342)/AP,PRN
E LEHMAN P/AU
L2 52 S E3-E7,E9-E12
E LEHMANN P/AU
L3 267 S E3-E6,E11-E14
E OREDDIGER R/AU
E ROEDDIGER R/AU

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L4            9 S E3,E4
                E ROEDIGER R/AU
L5            2 S E4
                E RODIGER R/AU
L6            1 S E4
                E RODDIGER R/AU
L7            2 S E4
                E WALTER MATSUI/AU
L8            4 S E4,E5
                E MATSUI R/AU
L9           15 S E3
                E MATSUI W/AU
                SEL RN L1

     FILE 'REGISTRY' ENTERED AT 14:22:38 ON 23 AUG 2005
L10           7 S E1-E7
L11           6 S L10 AND ERYTHROPOIETIN
L12           1 S L10 NOT L11
                E ERYTHROPOIETIN
L13        1792 S E3
L14        1792 S L11,L13
                E IRON/CN
L15           1 S E3
                E FE/MF
L16          30 S E3 NOT MASS
L17          30 S L15,L16

     FILE 'HCAPLUS' ENTERED AT 14:24:56 ON 23 AUG 2005
L18        9810 S L14
L19       11804 S ?ERYTHROPOIETIN?
L20         129 S DARBEPOETIN?(S)(ALPHA OR ALFA)
L21         135 S ?DARBEPOETIN?
L22        6067 S EPO OR EPREX
L23         298 S EPOETIN?(S)(ALFA OR ALPHA)
L24         100 S EPOETIN?(S)BETA
L25         458 S EPOETIN
L26          42 S ARANESP
L27       14463 S L18-L26
L28         655 S L27 AND L17
L29        1236 S L27 AND (FE OR IRON)
L30        1243 S L28,L29
                E HEART DISEASE/CT
                E E4+ALL
                E E2+ALL
L31       86736 S E7+OLD,NT
L32          29 S L30 AND L31
L33           0 S E90+OLD,NT AND L30
L34          47 S E92+OLD,NT AND L30
L35          36 S L32,L34 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L36           1 S L32,L34 AND L1-L9
L37           3 S L35 AND ?CONJUGAT?
L38           2 S L37 NOT 3/SC
L39           2 S L36,L38
L40          33 S L35 NOT L36-L39
                SEL DN AN 6-9 13-15 19-27
L41          16 S L40 AND E1-E48
L42          18 S L39,L41
L43         597 S ?RHUEPO?
L44         155 S L43 AND (L17 OR FE OR IRON)
L45           3 S L44 AND L31
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                E HEART, DISEASE/CT
                E E3+ALL
L46           5 S L44 AND E92+OLD,NT
L47           5 S L45,L46
L48           4 S L47 NOT 2005/PY
L49          19 S L42,L48 AND L1-L9,L18-L48
L50       14474 S L27,L43
L51         360 S L50 AND ?CONJUGAT?
L52         330 S L50 AND ?GLYCOSYLAT?
L53         194 S L50 AND (PEG OR PEGYLAT?)
L54          55 S L50 AND (POLYOXYETHYLENE OR POLYETHYLENEGLYCOL OR POLYETHYLEN
L55           4 S L50 AND POLY()(OXYETHYLENE OR ETHYLENEGLYCOL OR ETHYLENEOXIDE
L56          24 S L50 AND POLY()(OXY ETHYLENE OR ETHYLENE GLYCOL OR ETHYLENE OX
L57         237 S L50 AND (POLYOXY ETHYLENE OR POLYETHYLENE GLYCOL OR POLYETHYL
L58         316 S L50 AND POLYOXYALKYLENE

     FILE 'REGISTRY' ENTERED AT 14:42:28 ON 23 AUG 2005
L59           1 S 25322-68-3
L60           0 S L14 AND C2H4O

     FILE 'HCAPLUS' ENTERED AT 14:42:46 ON 23 AUG 2005
L61         266 S L50 AND L59
L62         986 S L51-L58,L61
L63         804 S L62 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L64          32 S L63 AND (L17 OR FE OR IRON)
L65          30 S L64 AND L18

     FILE 'REGISTRY' ENTERED AT 14:44:41 ON 23 AUG 2005
L66           1 S L14 AND NC4/ES
L67          11 S L14 AND S/ELS

     FILE 'HCAPLUS' ENTERED AT 14:45:59 ON 23 AUG 2005
L68       12350 S L27 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L69        1036 S L68 AND (L17 OR FE OR IRON)
L70        1808 S L63-L65,L69
L71        1808 S L70 OR L70
L72         500 S L71  RAN=(2001:686932,)
L73         500 S L71  RAN=(1997:740129,2001:679500)
L74         808 S L71  RAN=(,1997:730870)

     FILE 'REGISTRY' ENTERED AT 14:48:11 ON 23 AUG 2005

     FILE 'HCAPLUS' ENTERED AT 14:48:17 ON 23 AUG 2005
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L75          SEL L74 1- RN :    3039 TERMS
                SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 14:48:35 ON 23 AUG 2005
L76        3035 S L75

     FILE 'HCAPLUS' ENTERED AT 14:48:58 ON 23 AUG 2005
                SET SMARTSELECT ON
L77          SEL L73 1- RN :    4980 TERMS
                SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 14:49:13 ON 23 AUG 2005
L78        4980 S L77

     FILE 'HCAPLUS' ENTERED AT 14:49:40 ON 23 AUG 2005
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L79          SEL L72 1- RN :   43982 TERMS
                 SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 14:50:18 ON 23 AUG 2005
L80        43982 S L79
L81        49174 S L76,L78,L80
L82          455 S L81 AND C2H4O
L83           55 S L82 AND NC4/ES
L84            1 S L83 AND S/ELS
L85           54 S L83 NOT L84
L86              STR
L87           50 S L86
L88              STR L86
L89           50 S L88
L90        15844 S L86 FUL
L91           86 S L90 AND C2H4O
L92           28 S L91 AND 1/NR NOT P/ELS
                 SEL RN 4 6-9 22 28
L93            7 S L92 AND E1-E7
L94           58 S L91 NOT L92
L95           35 S L94 NOT P/ELS

     FILE 'HCAPLUS' ENTERED AT 15:13:34 ON 23 AUG 2005
L96            8 S L93
L97            0 S L96 AND L50
L98          136 S L51,L52 AND L53-L58,L61
L99          110 S L98 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L100          18 S L99 AND L51 AND L52
L101           0 S L100 AND L31
L102           6 S L98 AND L31
L103           4 S L99 AND L31
L104           6 S L102,L103
L105          18 S L100 NOT L104
                 SEL DN AN 3 7 9 12 13 15 16 17
L106           8 S E8-E31 AND L105
                 SEL DN AN L48 1 4
L107           2 S L48 AND E32-E37
L108          27 S L49,L106,L107
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:23:50 ON 23 AUG 2005
L109          19 S E38-E56
L110          15 S L109 AND L14
L111           3 S L109 AND L17
L112           1 S L109 AND L59

     FILE 'HCAPLUS' ENTERED AT 15:25:04 ON 23 AUG 2005

     FILE 'REGISTRY' ENTERED AT 15:25:36 ON 23 AUG 2005

     FILE 'WPIX' ENTERED AT 15:26:21 ON 23 AUG 2005
L113        1961 S L19/BI,ABEX OR L20/BI,ABEX OR L21/BI,ABEX OR L22/BI,ABEX OR L
L114         570 S (B04-H07 OR C04-H07)/MC
                 E ERYTHROPOIETIN/CN
L115           7 S E3-E9
                 E DARBEPOETIN/CN
L116           1 S E4,E5
L117           8 S L115,L116
                 SEL SDCN
                 EDIT /SDCN /DCN
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L118        653 S E1-E8
L119        213 S C07K014-505/IPC
L120       2084 S L113,L114,L118,L119
L121        101 S L120 AND A61K047-48/IPC
L122         29 S L120 AND A05-H03?/MC
L123         98 S L120 AND (B04-C03C OR C04-C03C)/MC
                E PEG/CN
L124          2 S E3
L125      10737 S (RA0GM6 OR R02044)/DCN OR 2044/DRN
L126        136 S L120 AND L125
L127         33 S L121 AND L122,L123,L126
L128          2 S L127 AND A61P009/IPC
L129         14 S L127 AND (B14-F? OR C14-F? OR B12-F? OR C12-F?)/MC
L130         15 S L128,L129
                SEL DN AN 6 7 9 11 12
L131          5 S E1-E10 AND L130

     FILE 'WPIX' ENTERED AT 15:36:08 ON 23 AUG 2005

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